Epilepsy Syndromes with Onset at a Variable Age

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Co-Chair – Nosology and Definitions Task Force, ILAE

Objectives

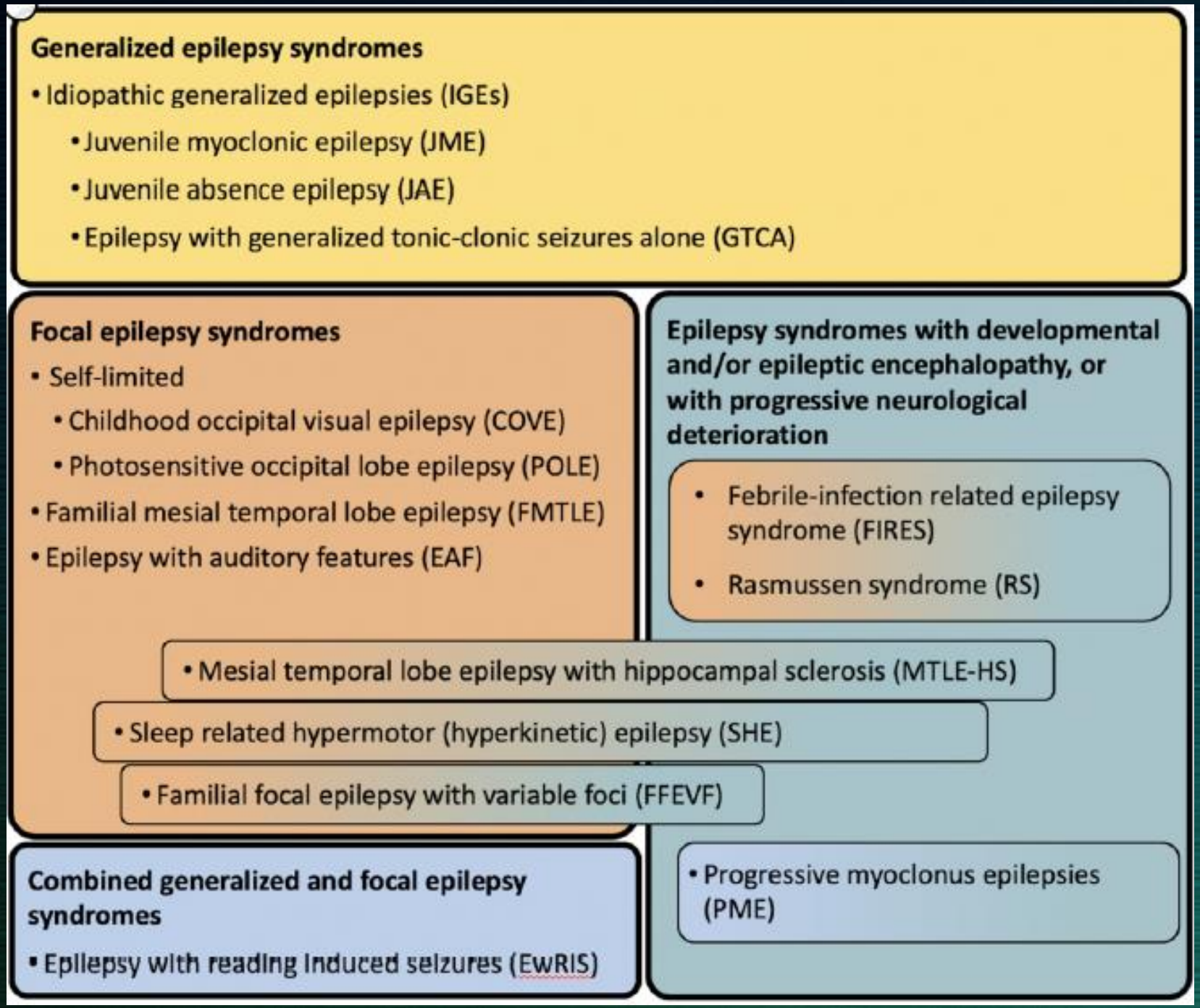
What is meant by “onset at a variable age”?

How do we classify these syndromes?

What are the diagnostic criteria for each syndrome?

At a Variable Age

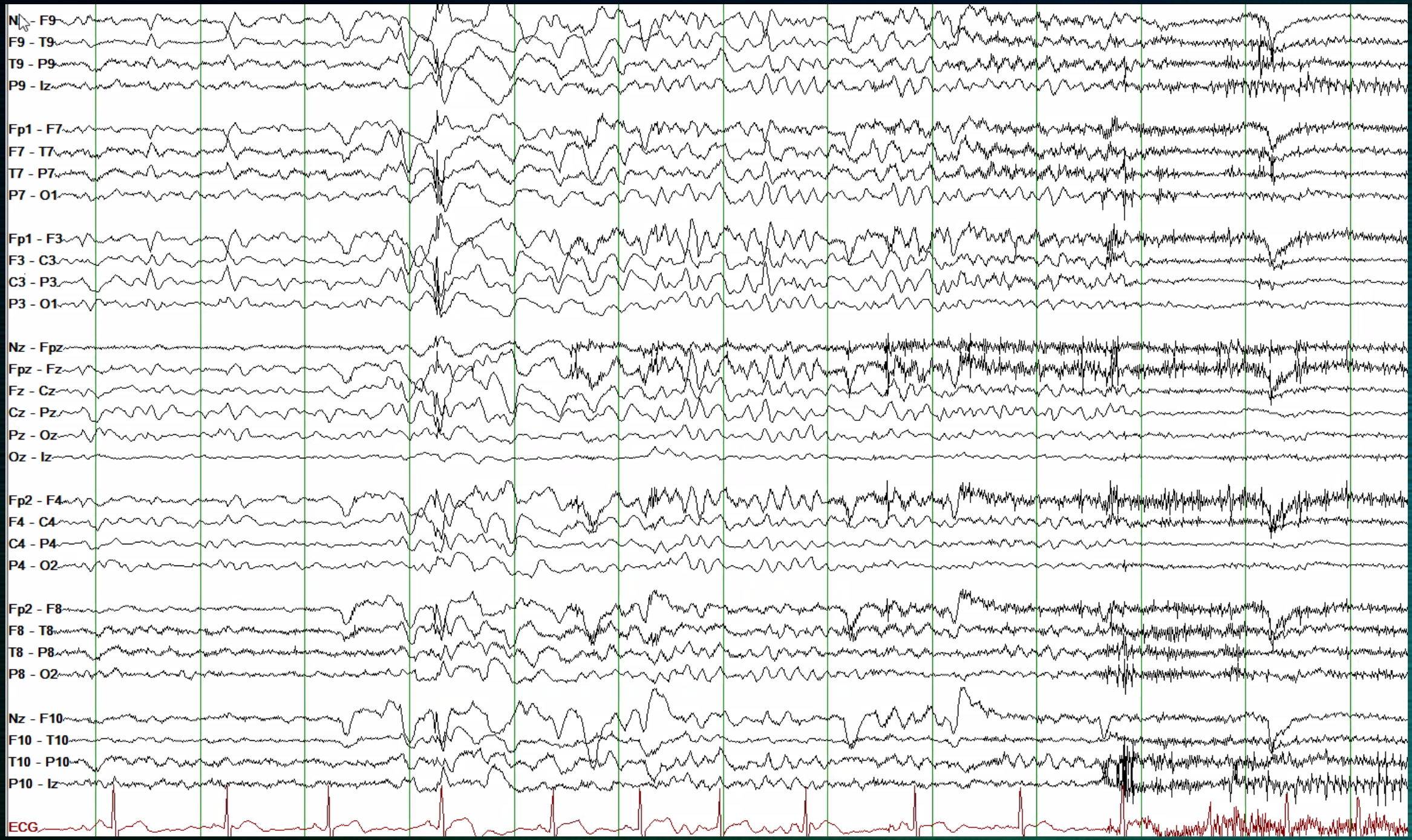
Syndromes that can begin both in pediatrics (≤18 years) and adulthood (≥19 years)

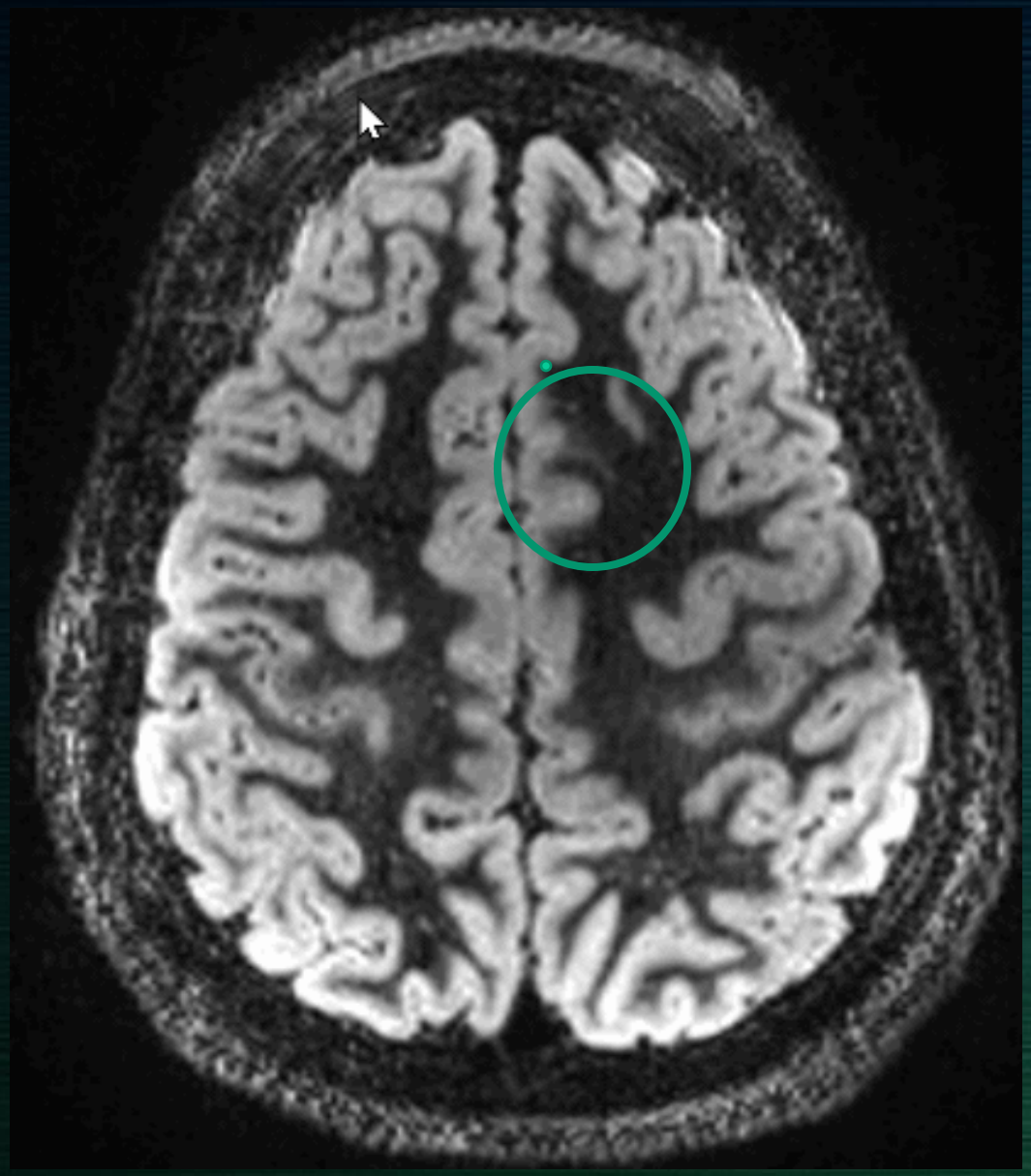

Generalized epilepsy syndromes
• Idiopathic generalized epilepsies (IGEs)
• Juvenile myoclonic epilepsy (JME)
• Juvenile absence epilepsy (JAE)
• Epilepsy with generalized tonic-clonic seizures alone (GTCA)
Focal epilepsy syndromes
• Self-limited
• Childhood occipital visual epilepsy (COVE)
• Photosensitive occipital lobe epilepsy (POLE)
• Familial mesial temporal lobe epilepsy (FMTLE)
• Epilepsy with auditory features (EAF)
• Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS)
• Sleep related hypermotor (hyperkinetic) epilepsy (SHE)
• Familial focal epilepsy with variable foci (FFEVF)
Epilepsy syndromes with developmental and/or epileptic encephalopathy, or with progressive neurological deterioration
• Febrile-infection related epilepsy syndrome (FIRES)
• Rasmussen syndrome (RS)
• Progressive myoclonus epilepsies (PME)
Combined generalized and focal epilepsy syndromes
• Epilepsy with reading induced seizures (EwRIS)

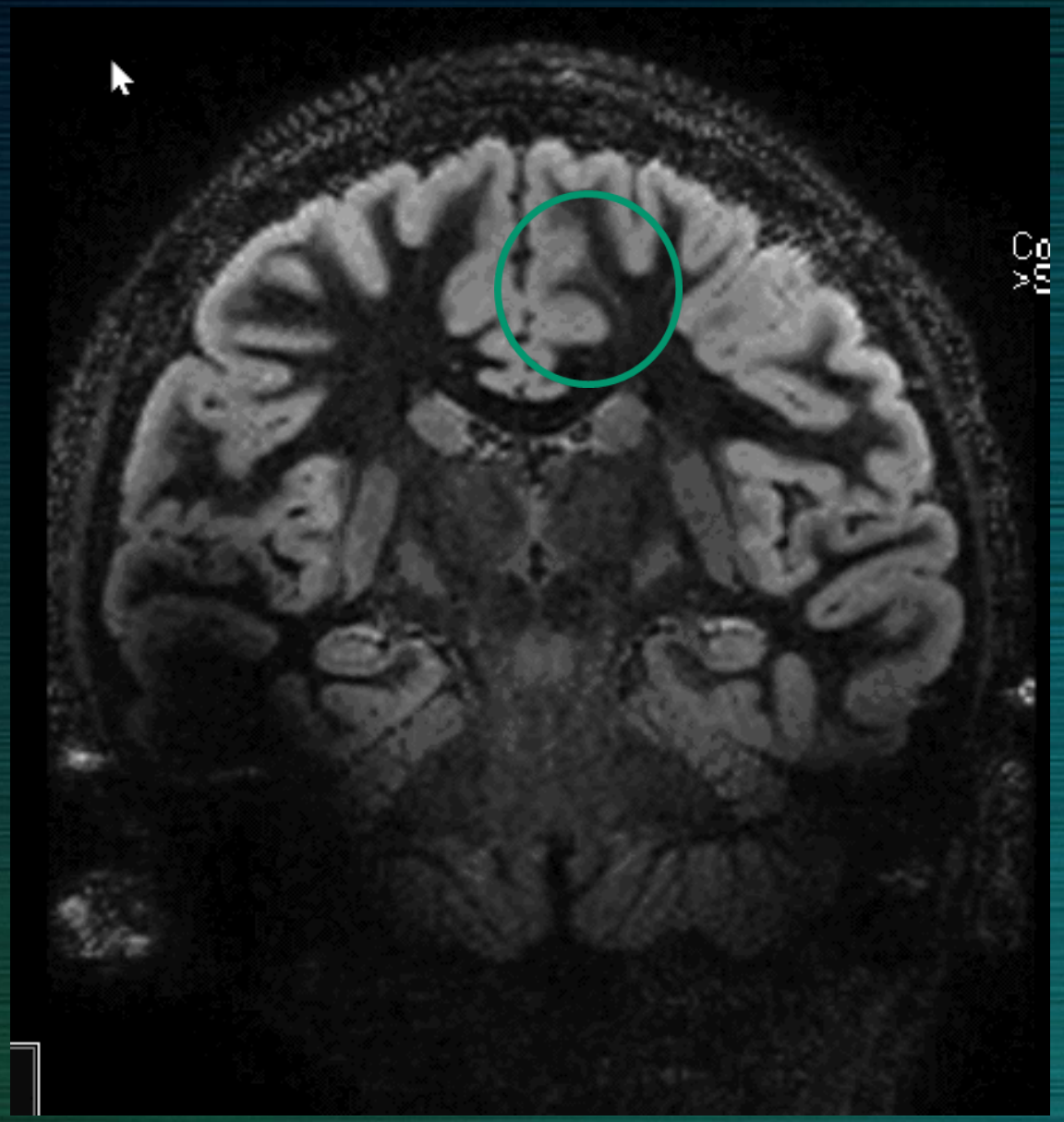
Focal Epilepsy Syndromes

Sleep-related hypermotor (hyperkinetic) epilepsy (SHE)

	Mandatory	**Alert**	**Exclusionary**
Seizures	Brief, focal motor seizures with hyperkinetic or asymmetric tonic/dystonic features seen mostly in sleep	Seizures predominantly from the awake state	Seizures ONLY during wakefulness Generalized onset seizures
EEG		Frequent discharges outside of frontal regions Generalized discharges	
Age at onset		<10 years or >20 years	<2 months or >64 years
Development at onset		Moderate to severe ID	
Exam		Focal abnormalities on neuro exam	
An MRI is not required for diagnosis of the syndrome but should be done to evaluate underlying etiology			
An ictal EEG is not required for diagnosis			


N - F9
F9 - T9
T9 - P9
P9 - Iz
Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Nz - Fpz
Fpz - Fz
Fz - Cz
Cz - Pz
Pz - Oz
Oz - Iz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
Nz - F10
F10 - T10
T10 - P10
P10 - Iz
ECG





Familial Mesial Temporal Lobe Epilepsy

	Mandatory	**Alert**	**Exclusionary**
Seizures	Focal cognitive (esp déjà vu), sensory or autonomic seizures		Generalized onset seizures
EEG		Generalized discharges	
Development at onset		ID	
Exam		Focal abnormalities on neuro exam	
Imaging	Normal or hippocampal atrophy/sclerosis		
Family history	Family history of individuals with focal seizures that arise from the mesial temporal lobe		
An MRI is required for diagnosis to exclude other causes			
An ictal EEG is not required for diagnosis			

Familial Focal Epilepsy with Variable Foci

	Mandatory	**Alert**	**Exclusionary**
Seizures	Focal onset seizures		Generalized onset seizures
EEG		Generalized discharges	
Age at onset		Neonatal onset	
Development at onset			Moderate to profound ID
Neurological exam		Focal neurological abnormalities	
Imaging	Normal or focal cortical dysplasia		
Family history	Family history of persons with focal seizures that arise from cortical regions that differ between family members		Family history of focal seizures that occur exclusively before 20 months of age
An MRI is required for diagnosis, as family history of focal seizures may be incidental, due to an acquired cause			
An ictal EEG is not required for diagnosis			

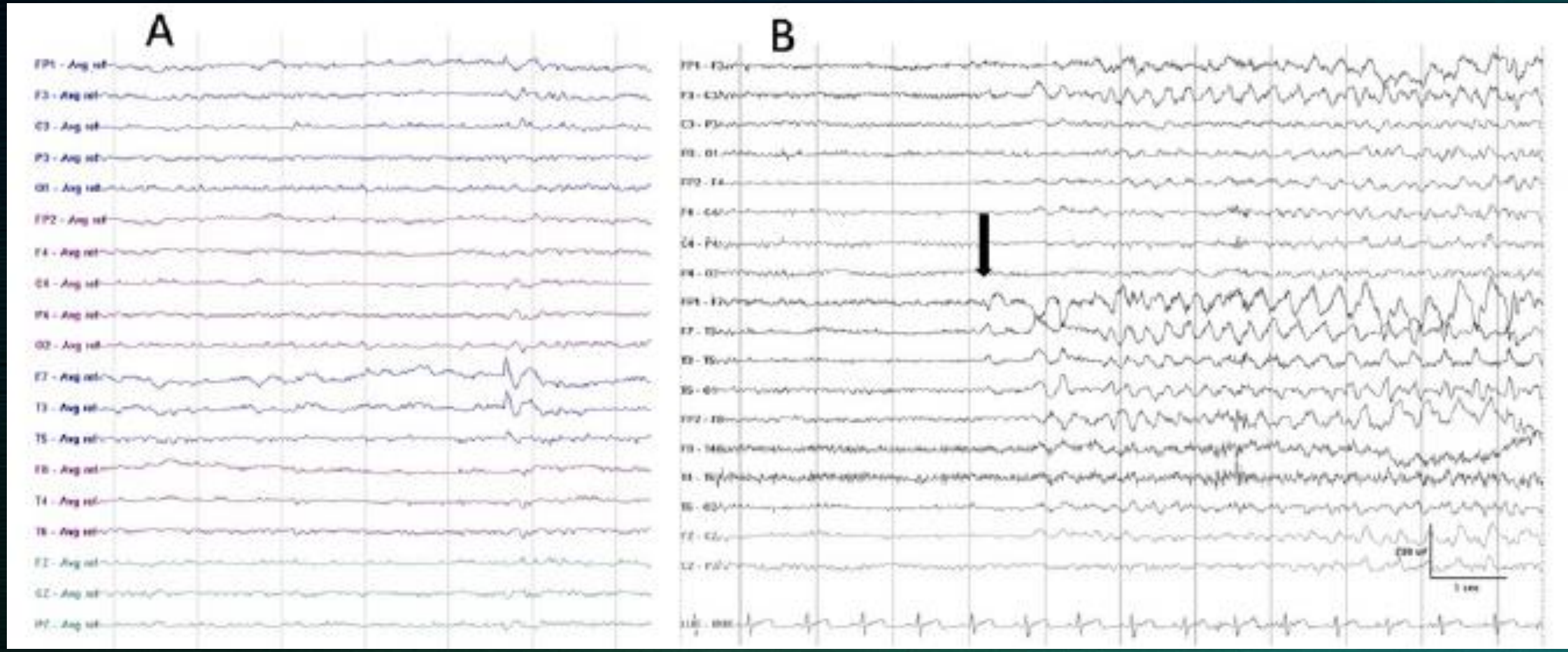
Look carefully for genetic variant that may also result in FCD – DEPDC5, NPRL2, NPRL3, TSC1 or 2

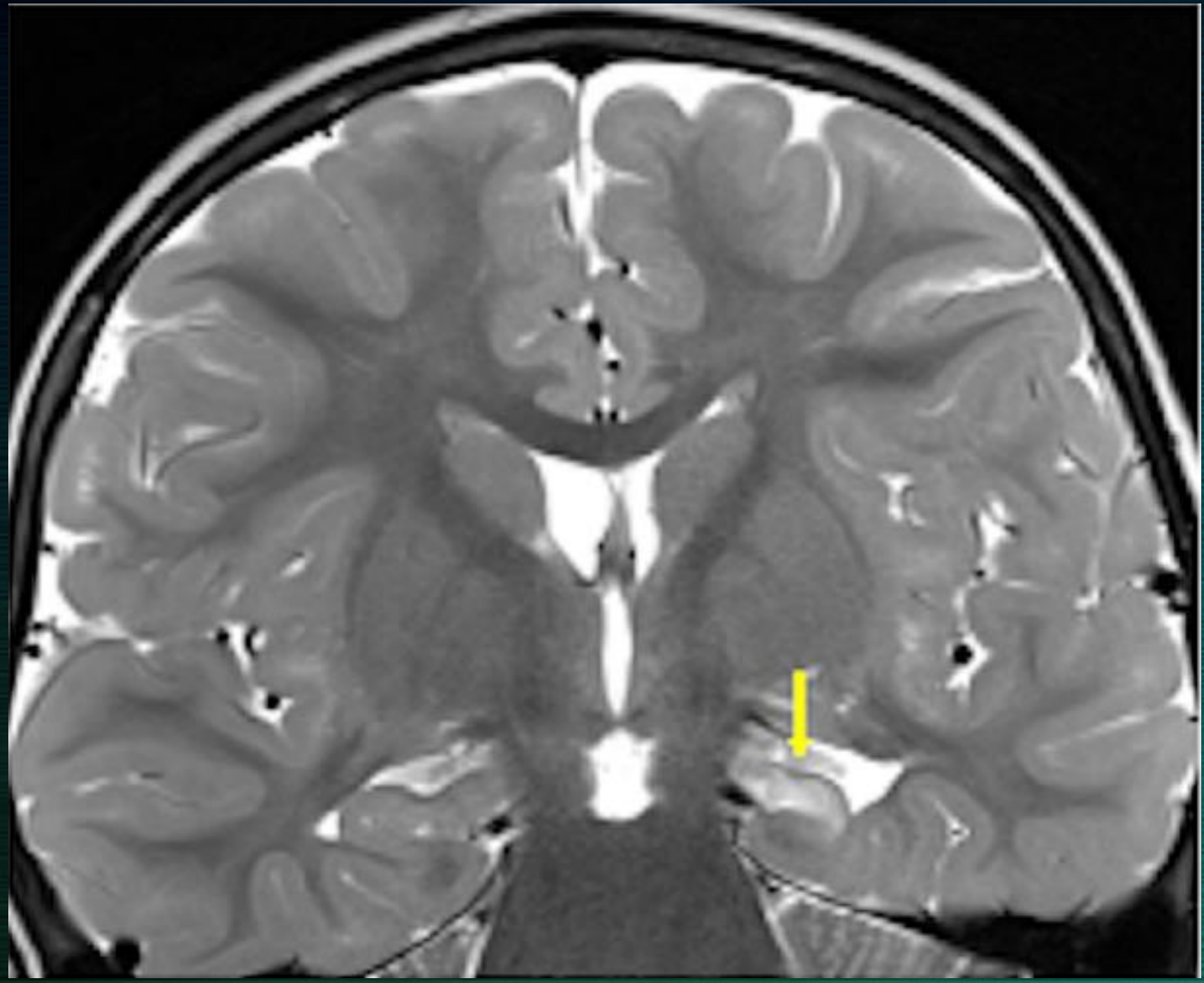
Epilepsy with Auditory Features

	Mandatory	**Alert**	**Exclusionary**
Seizures	Focal sensory auditory seizures and/or focal cognitive seizures with receptive aphasia		Generalized onset seizures Other focal onset seizures
EEG		Generalized discharge	
Development at onset			Moderate to severe ID
Neurological exam		Focal neurological abnormalities	
Imaging	Normal or focal cortical dysplasia		
An MRI is required for diagnosis to exclude other causes			
An ictal EEG is not required for diagnosis			

Mesial Temporal Lobe Epilepsy with HS

	Mandatory	**Alert**	**Exclusionary**
Seizures	Focal aware or impaired awareness seizures with initial semiology referable to mesial temporal lobe networks	Initial semiology refereable to networks other than mesial temporal	Generalized onset seizures
EEG		Consistent absence of temporal discharge despite repeated EEG Generalized discharge High amplitude centrotemporal spikes Discharges or focal slowing outside the temporal region	Recorded seizures with generalized onset Recorded seizures with onset outside of temporal lobe
Age at onset		<2 years	
Development at onset		Moderate to severe ID	
Neurological exam		Focal findings such as hemiparesis	
Imaging	Hippocampal sclerosis on MRI		
An MRI with hippocampal sclerosis is mandatory for diagnosis			
An ictal EEG is not required for diagnosis			

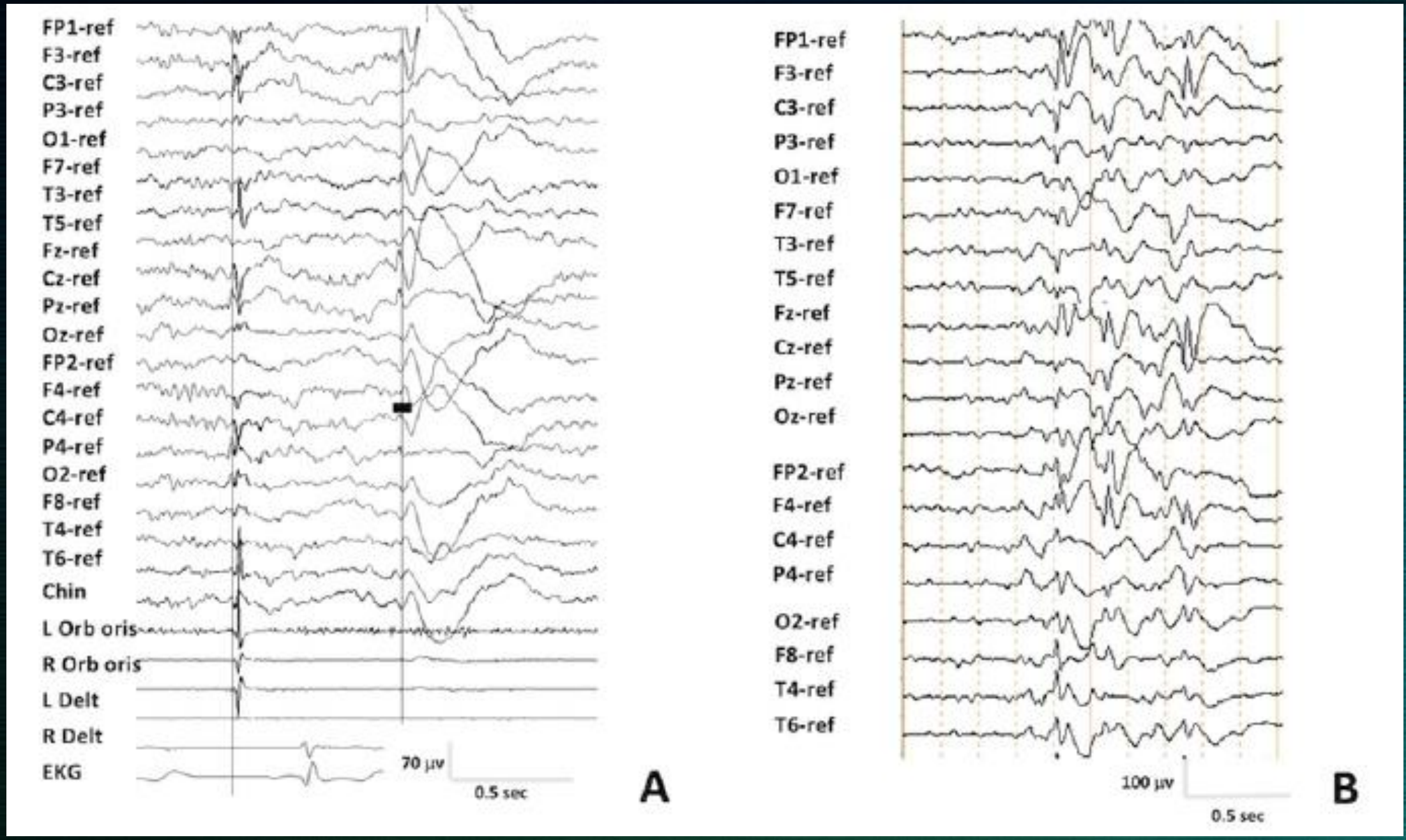

A
B



Combined Focal and Generalized

Epilepsy with Reading-Induced Seizures

	Mandatory	**Alert**	**Exclusionary**
Seizures	Reflex myoclonic seizures affecting orofacial muscles, triggered by reading or language-related tasks	Prominent myoclonic jerks affecting upper limbs	All other seizure types except GTCS
EEG			Background slowing excluding the postictal phase of a GTCS
Age at onset		>20 years	
Development at onset	Normal		
Neurological exam	Normal		
Imaging	Normal		
An MRI is required for diagnosis to exclude a structural cause			
An ictal EEG is not required, however observation during reading is highly recommended as it shows the characteristic myoclonus affecting orofacial muscles			


FP1-ref
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C3-ref
P3-ref
O1-ref
F7-ref
T3-ref
T5-ref
Fz-ref
Cz-ref
Pz-ref
Oz-ref
FP2-ref
F4-ref
C4-ref
P4-ref
O2-ref
F8-ref
T4-ref
T6-ref
Chin
L Orb oris
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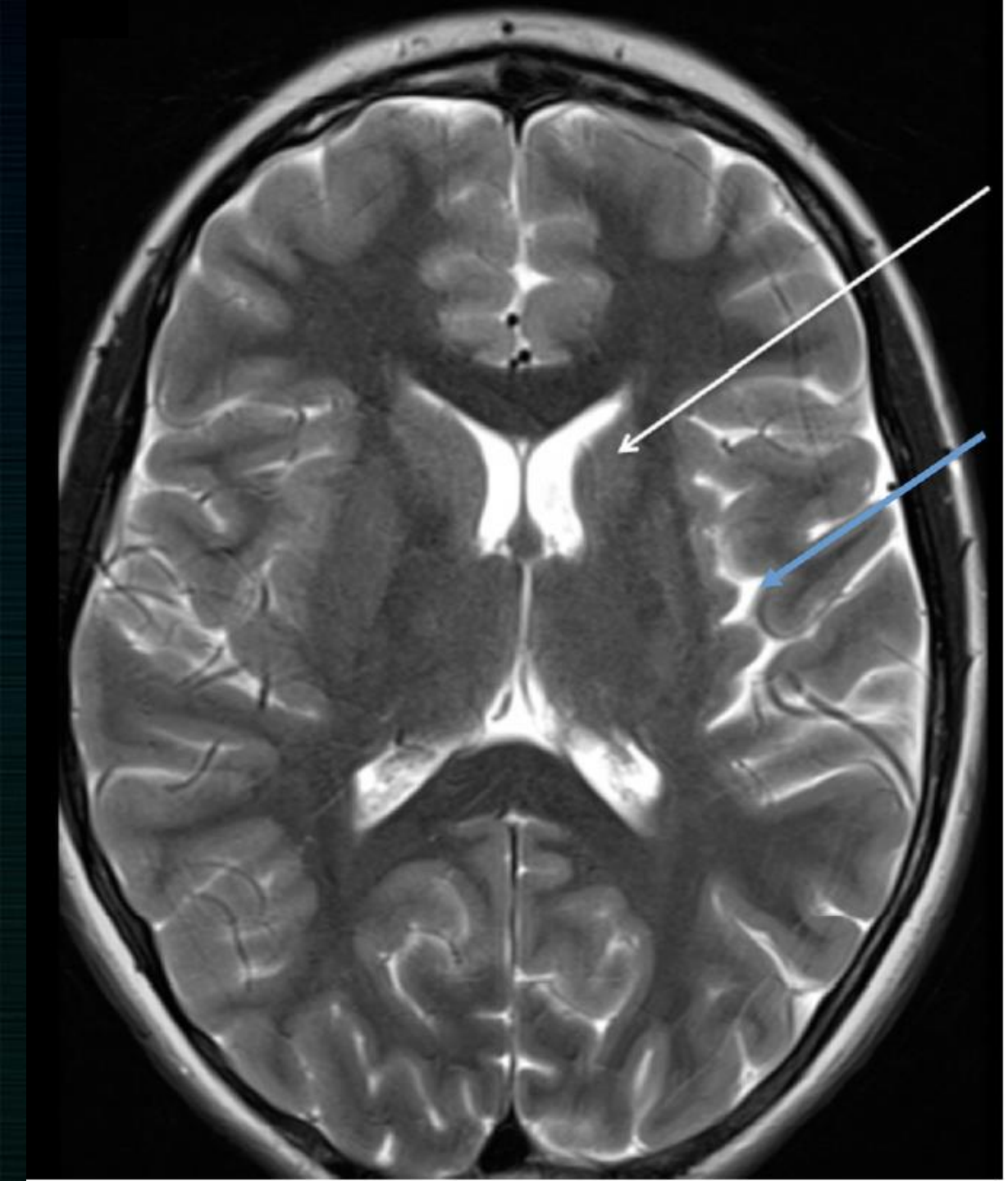
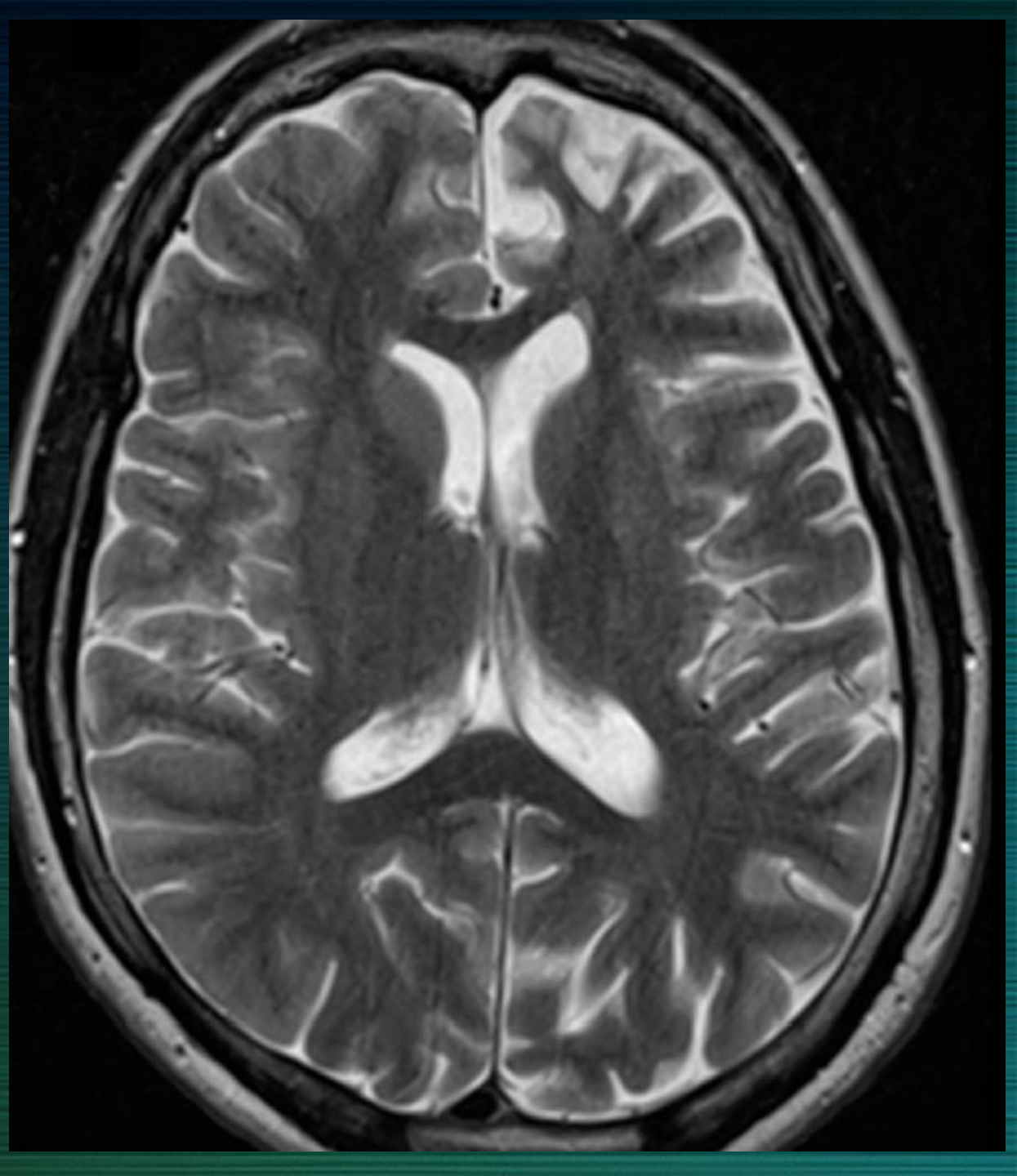
L Delt
R Delt
EKG
70 µv
0.5 sec
A
FP1-ref
F3-ref
C3-ref
P3-ref
O1-ref
F7-ref
T3-ref
T5-ref
Fz-ref
Cz-ref
Pz-ref
Oz-ref
FP2-ref
F4-ref
C4-ref
P4-ref
O2-ref
F8-ref
T4-ref
T6-ref
100 µv
0.5 sec
B

DEEs or Epilepsies with Progressive Neurological Deterioration

Rasmussen Syndrome

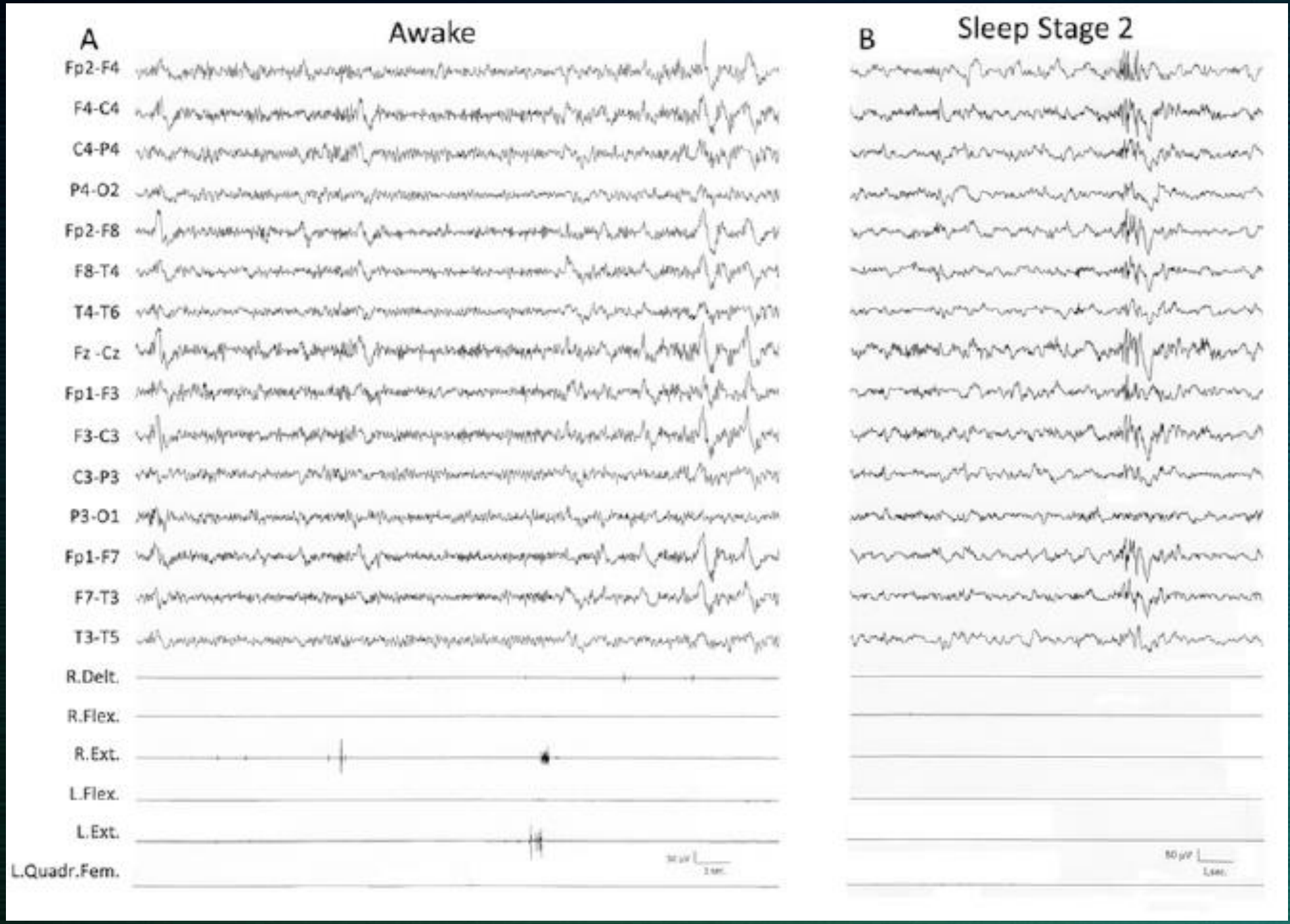
	Mandatory	**Alert**	**Exclusionary**
Seizures	Focal/hemispheric seizures which often increase in frequency over weeks to months	Focal onset indcpendently in both hemispheres	Generalized onset seizures
EEG	Hemispheric slowing and discharges	Generalized spike-wave	
Age at onset		Onset in adolescence or adulthood	
Development at onset		Delayed development prior to seizure onset	
Neurological exam			Hemiparesis present at seizure onset
Imaging	Progressive hemiatrophy (early insula and caudate head)	Lack of hyperintense signal and/or atrophy of ipsilateral caudate head and/or lack of hyperintense signal of grey or white matter	Imaging shows Sturge-Weber syndrome
Other			Metabolic cause of EPC Specific antibody-mediated encephalitis
Longterm outcome	DRE, progressive neuro deficits		
An MRI is required for diagnosis but an ictal EEG is not required			

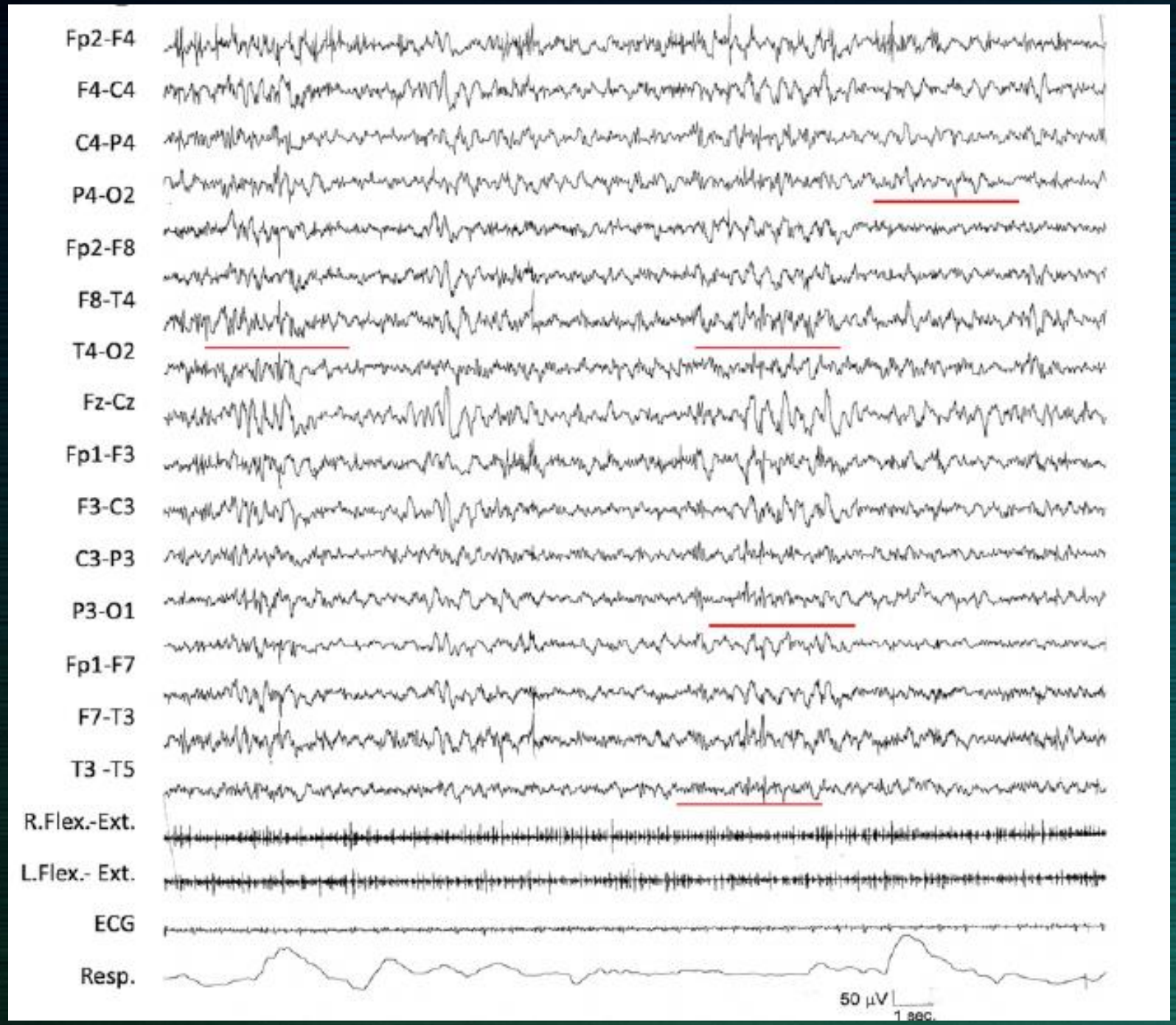




Progressive Myoclonus Epilepsy

	Mandatory	**Alert**	**Exclusionary**
Seizures	Myoclonic seizures		
EEG	Generalized spike and polyspike-wave		Persistent focal abnormalities, other than occipital
Age at onset	2-50 years	>20 years	
Development	Normal at onset		
Neurological exam	Normal at onset		
Comorbidities	Progressive neurocognitive deterioration over time		
Imaging	Normal at onset		
Course of illness	Progressive worsening of myoclonus, myoclonic and GTC seizures, cognitive decline, progressive cerebellar signs EEG deterioration with progressive slowing and/or increased discharges		


A
Awake
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
Fz -Cz
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
R.Delt.
R.Flex.
R.Ext.
L.Flex.
L.Ext.
L.Quadr.Fem.
B
Sleep Stage 2


Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-O2
Fz-Cz
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3 -T5
R.Flex.-Ext.
L.Flex.- Ext.
ECG
Resp.
50 µV
1 sec.

Summary

- Syndrome identification helps to hone diagnostic investigations, select best therapeutic options and provide more accurate prognosis regarding seizure outcome and risk of comorbidities

- Some syndromes onset at a variable age

- Most of these are focal epilepsies, some of which may be associated with DEE/progressive neurological deterioration

Idiopathic Generalised Epilepsies

J Helen Cross

The Prince of Wales's Chair of Childhood Epilepsy

UCL Great Ormond Street Institute of Child Health, London, UK

Outline

- History: how did we get here?,
- Idiopathic Generalised epilepsies within context of Genetic Generalised Epilepsies
- Diagnostic criteria

Edouard Hirsch

2005-2009 Commission Report
Epilepsia 2010;51:676-685

SPECIAL REPORT

Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009

*†Anne T. Berg, ‡Samuel F. Berkovic, §Martin J. Brodie, ¶Jeffrey Buchhalter, #**J. Helen Cross, ††Walter van Emde Boas, ‡‡Jerome Engel, §§Jacqueline French, ¶¶Tracy A. Glauser, ##Gary W. Mathern, ***Solomon L. Moshé, †Douglas Nordli, †††Perrine Plouin, and ‡Ingrid E. Scheffer

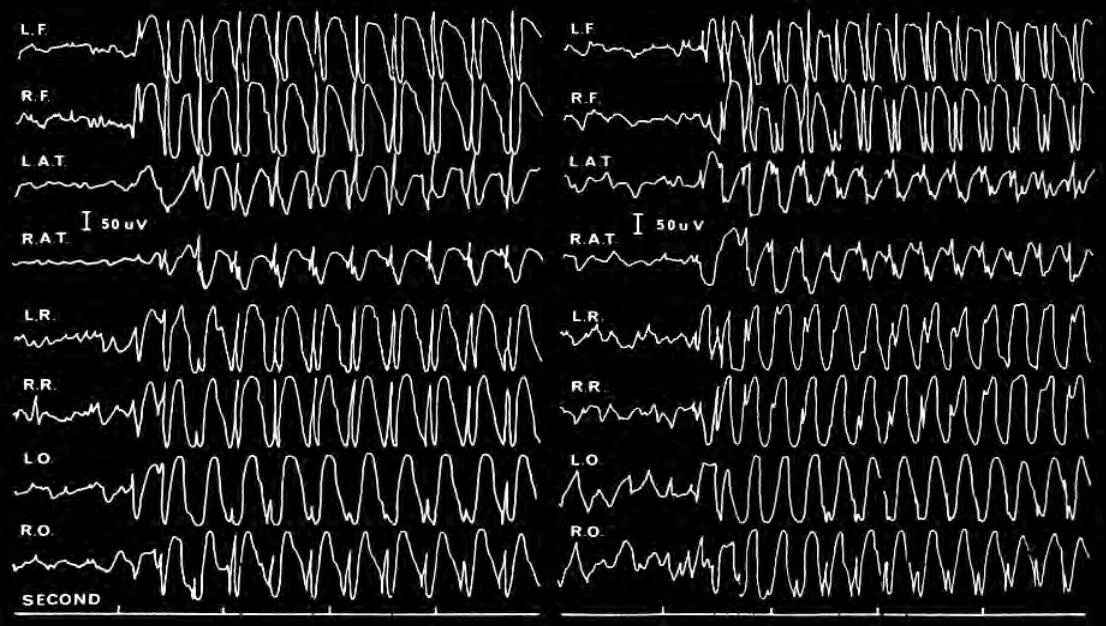
The term idiopathic was defined in the 1989 document:
'There is no underlying cause other than a possible hereditary predisposition…….
defined by age-related onset, clinical and electrographic characteristics, and a presumed genetic etiology.'

- highly pharmacoresponsive
- spontaneously remit during a predictable age range ……. unaccompanied by other consequences or disabilities, *although this is clearly not the case, as a variety of subtle cognitive and behavioral disorders are seen in association with these epilepsies.*

How do we know the Generalized Epilepsies are genetic?

Twins of William Lennox, 1950

Constance - Absence, onset 6 y - Kathryn



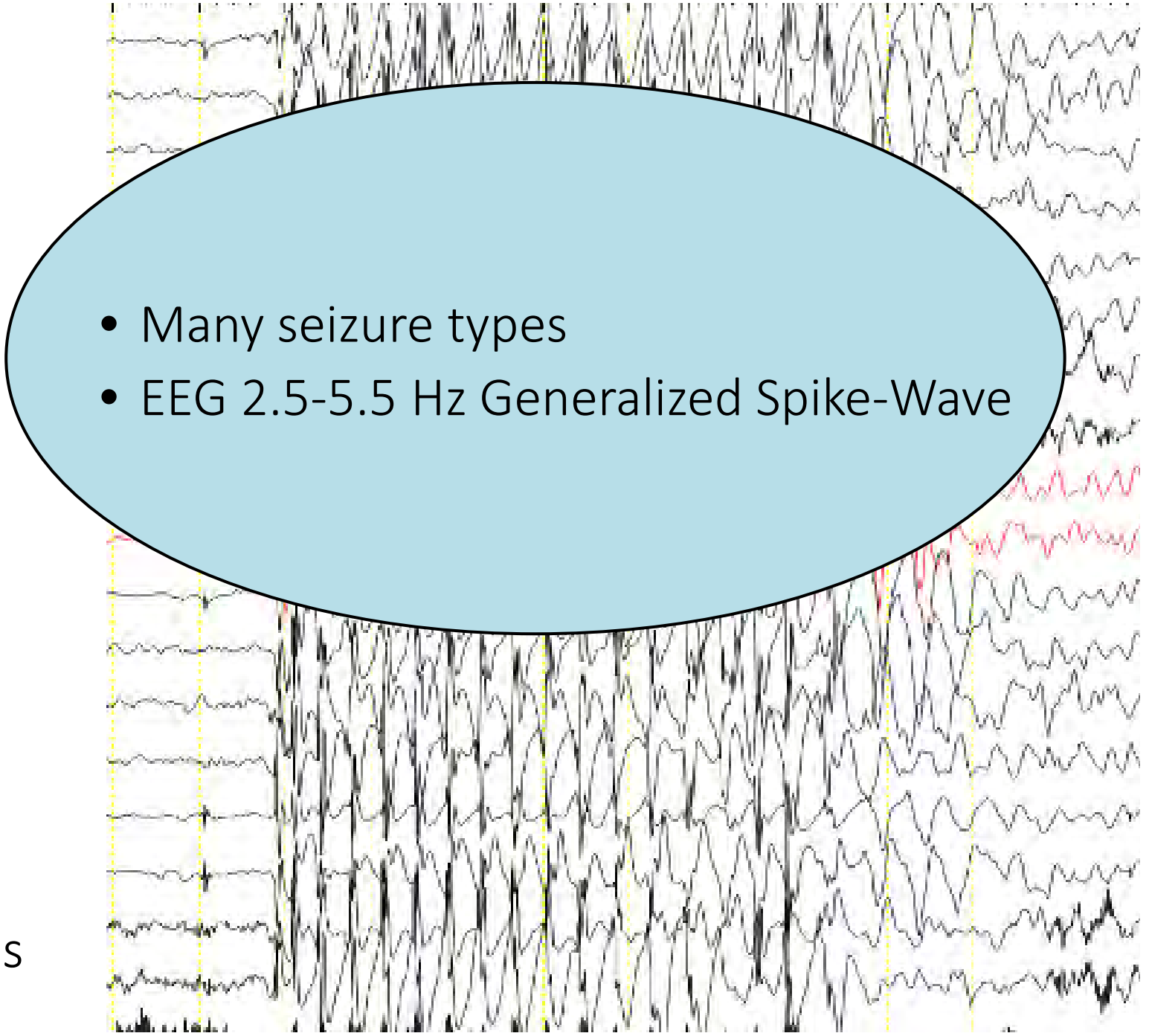
3 Hz Generalized Spike-Wave

2003: Seizure free since teenage

Courtesy of Ingrid Scheffer

Genetic Generalized Epilepsies

- Presumed genetic aetiology
- Broad group of patients
- Common and rare syndromes



- Many seizure types
- EEG 2.5-5.5 Hz Generalized Spike-Wave

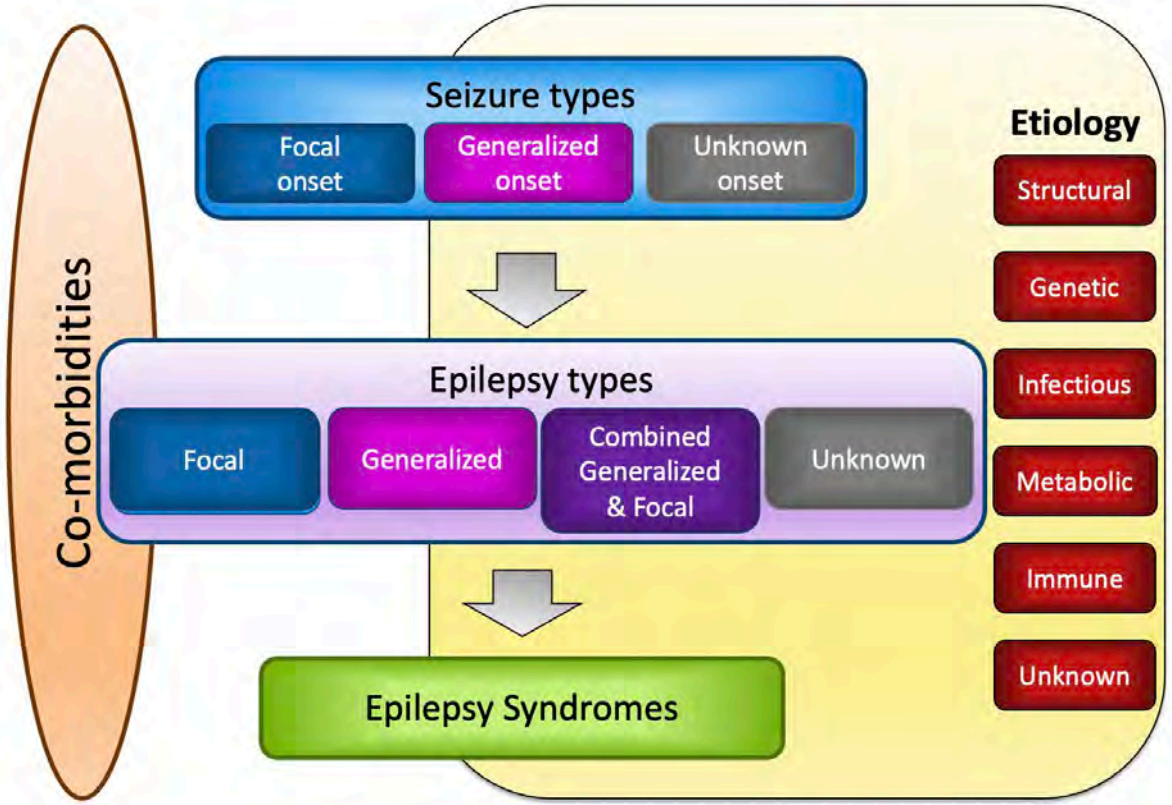
INTERNATIONAL LEAGUE AGAINST EPILEPSY

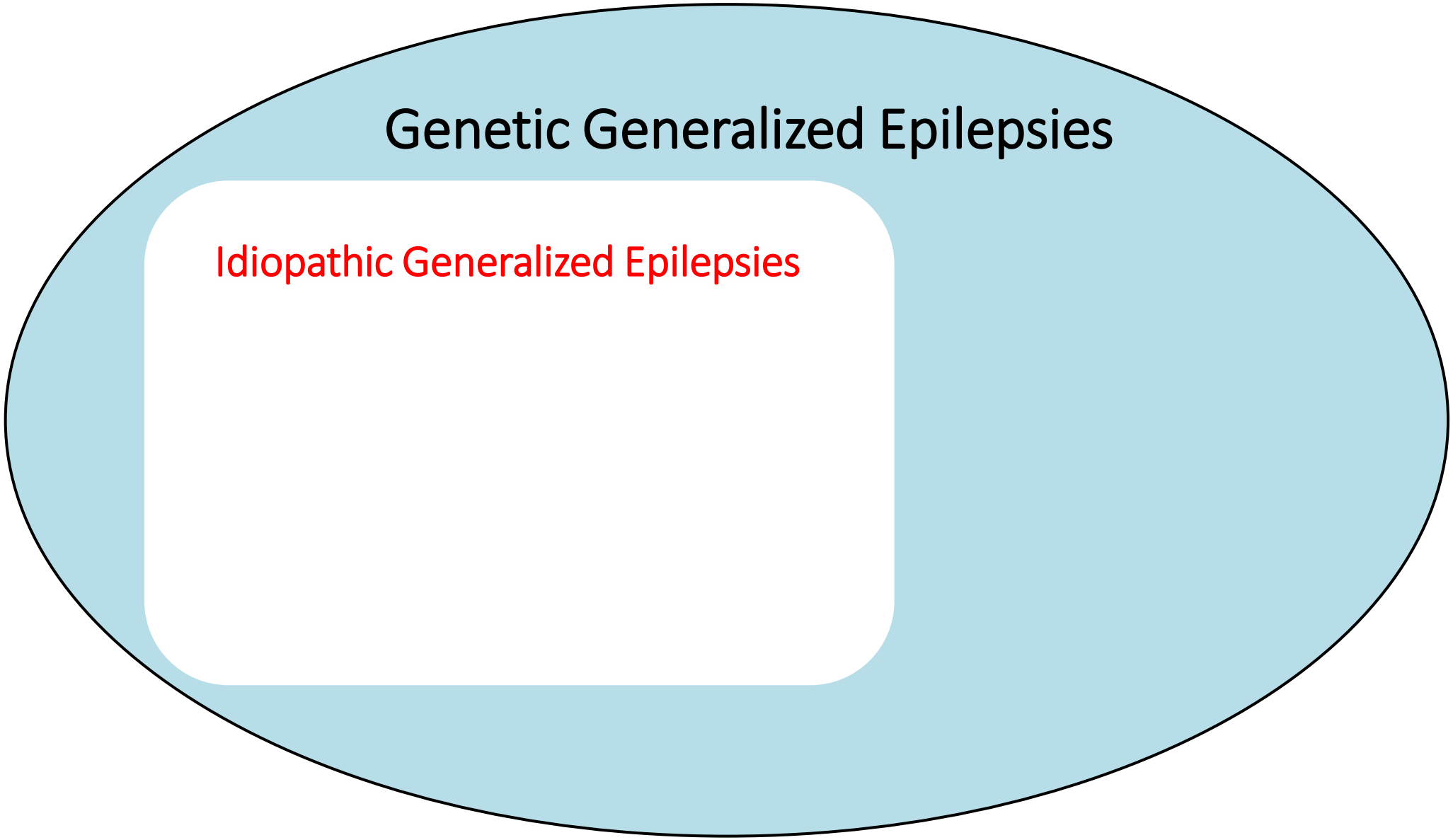
ILAE POSITION PAPER

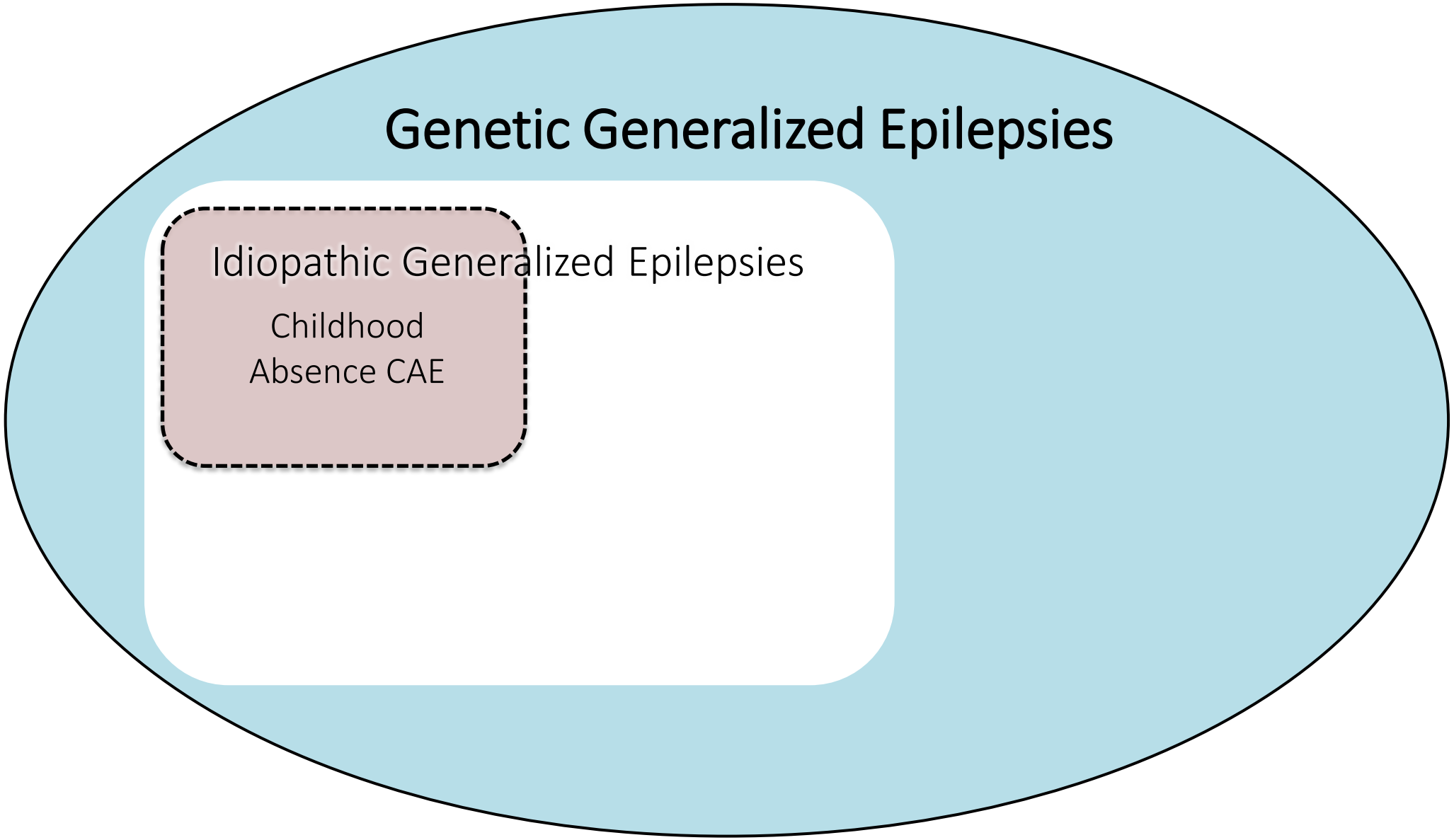
ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology

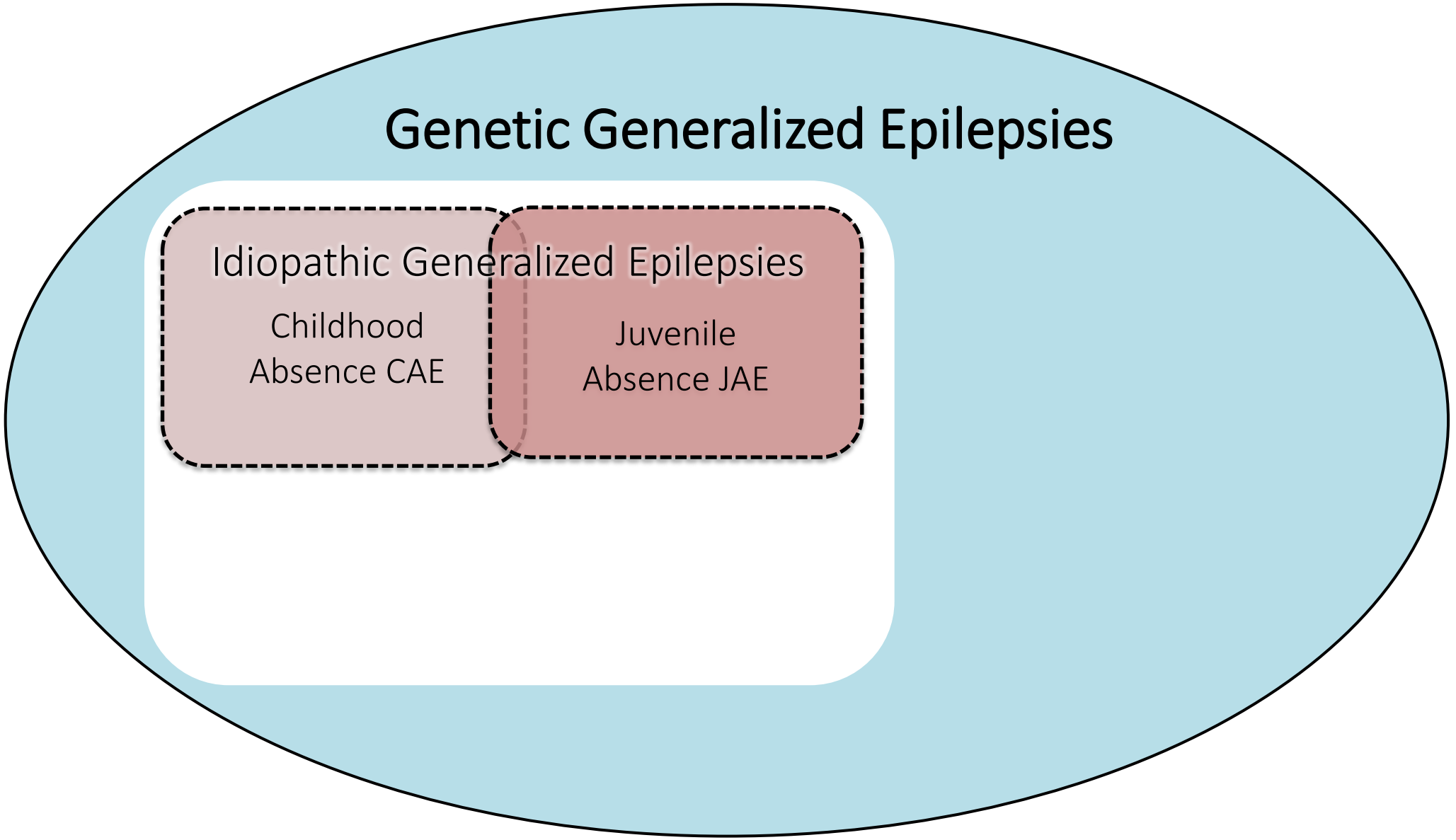
[1,2,3]Ingrid E. Scheffer, [1]Samuel Berkovic, [4]Giuseppe Capovilla, [5]Mary B. Connolly, [6]Jacqueline French, [7]Laura Guilhoto, [8,9]Edouard Hirsch, [10]Satish Jain, [11]Gary W. Mathern, [12]Solomon L. Moshé, [13]Douglas R. Nordli, [14]Emilio Perucca, [15]Torbjörn Tomson, [16]Samuel Wiebe, [17]Yue-Hua Zhang, and [18,19]Sameer M. Zuberi

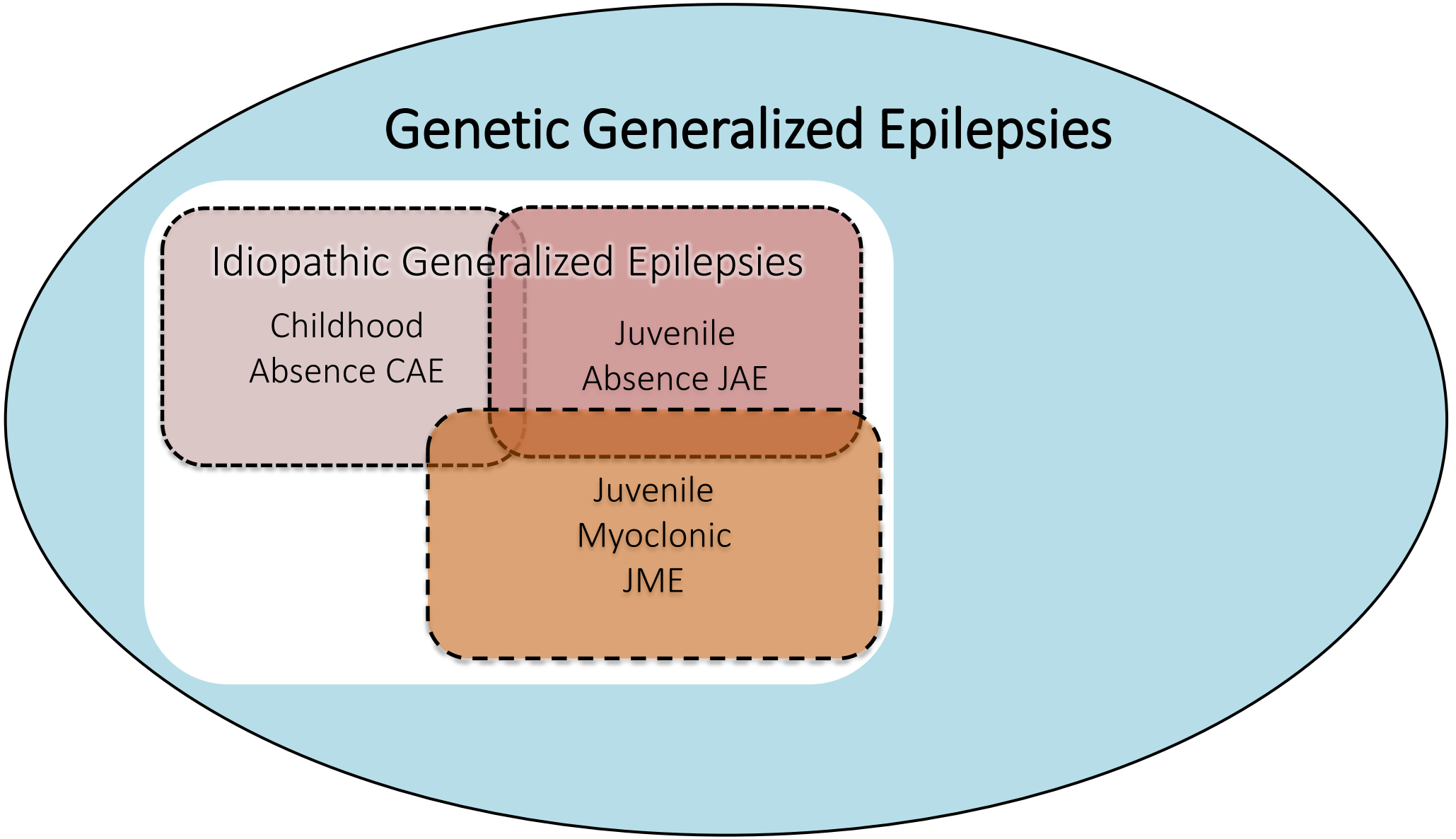
Epilepsia, 58(4):512–521, 2017
doi: 10.1111/epi.13709

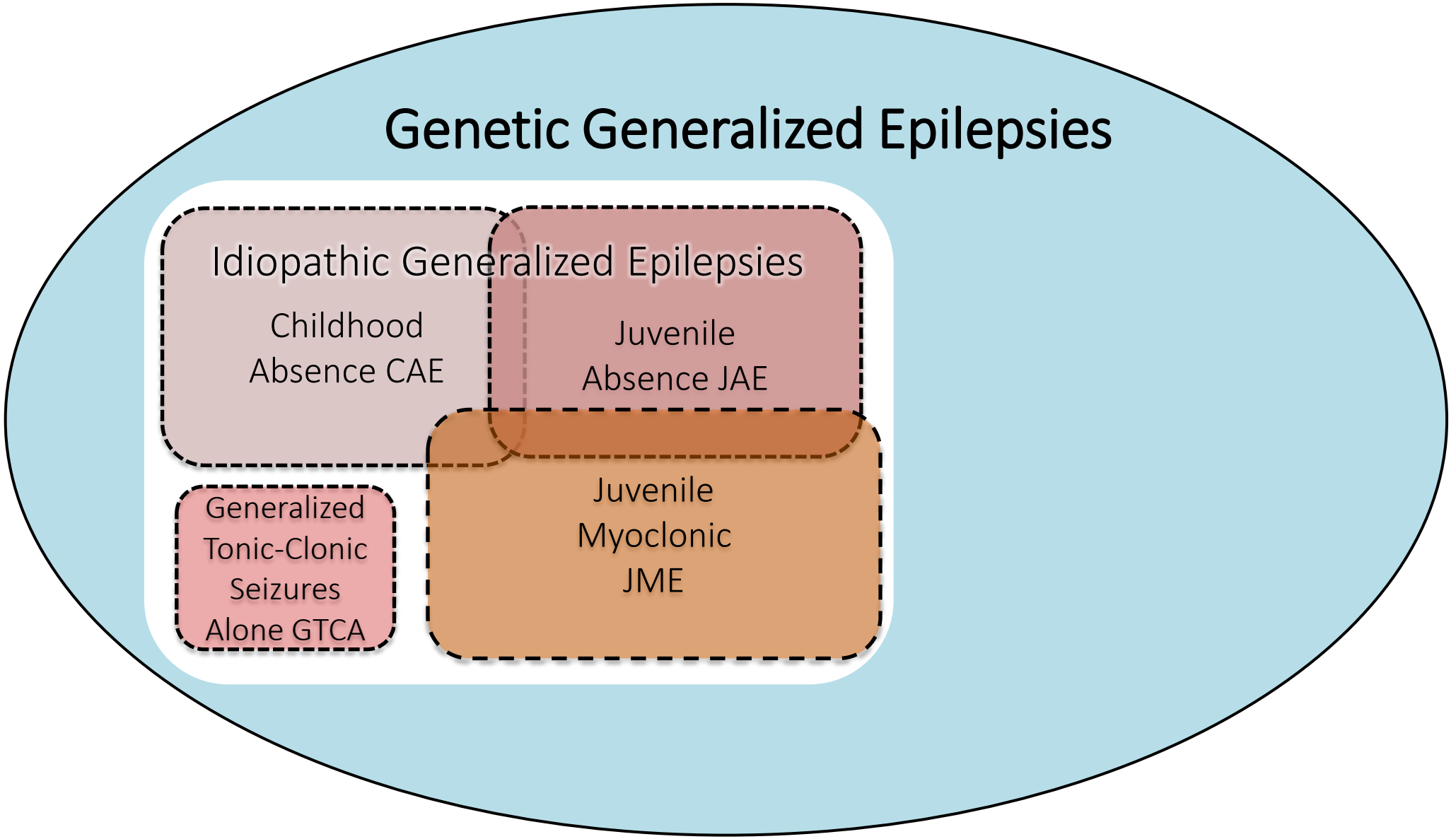


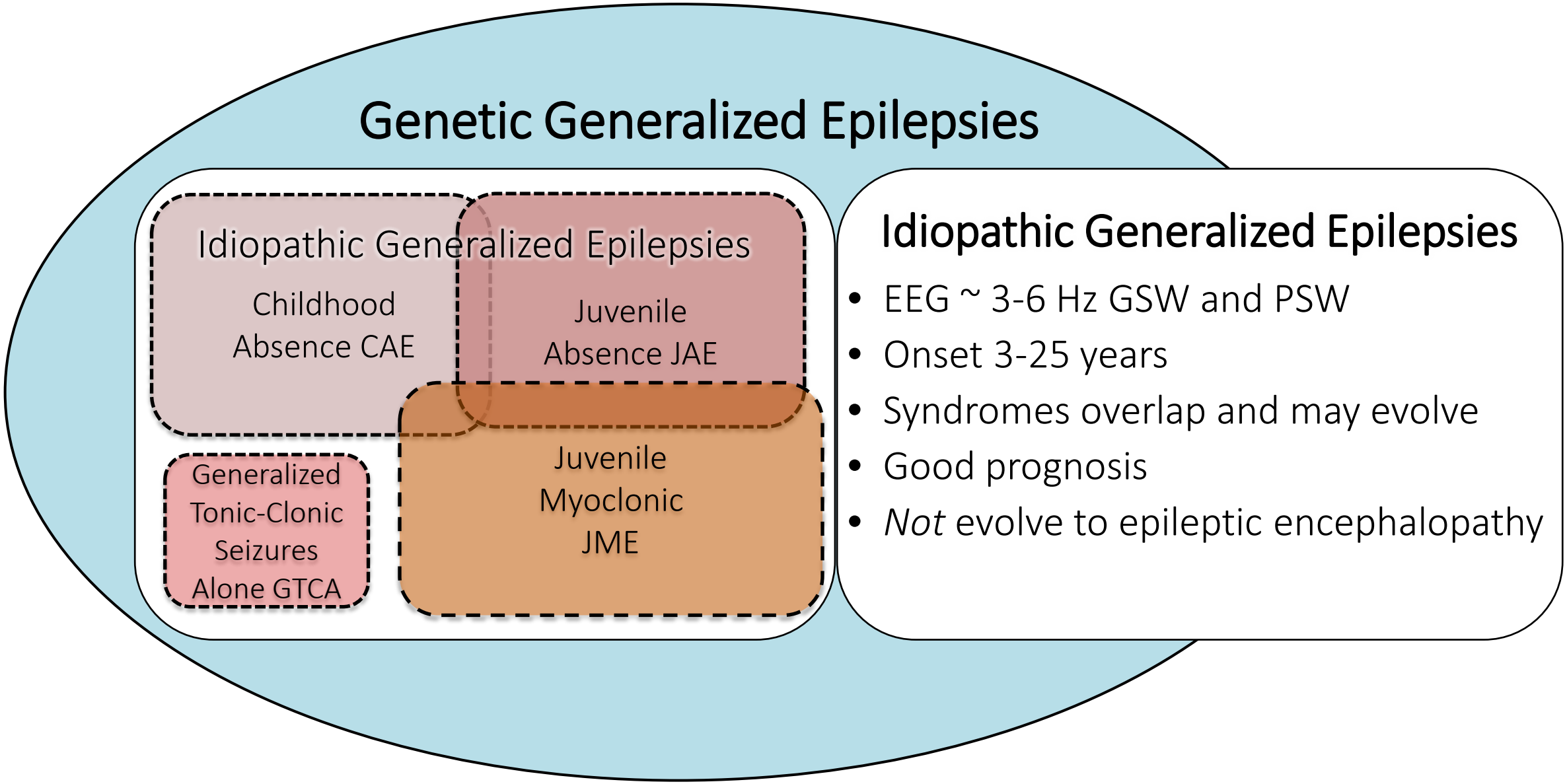

Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies


Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies
Childhood
Absence CAE

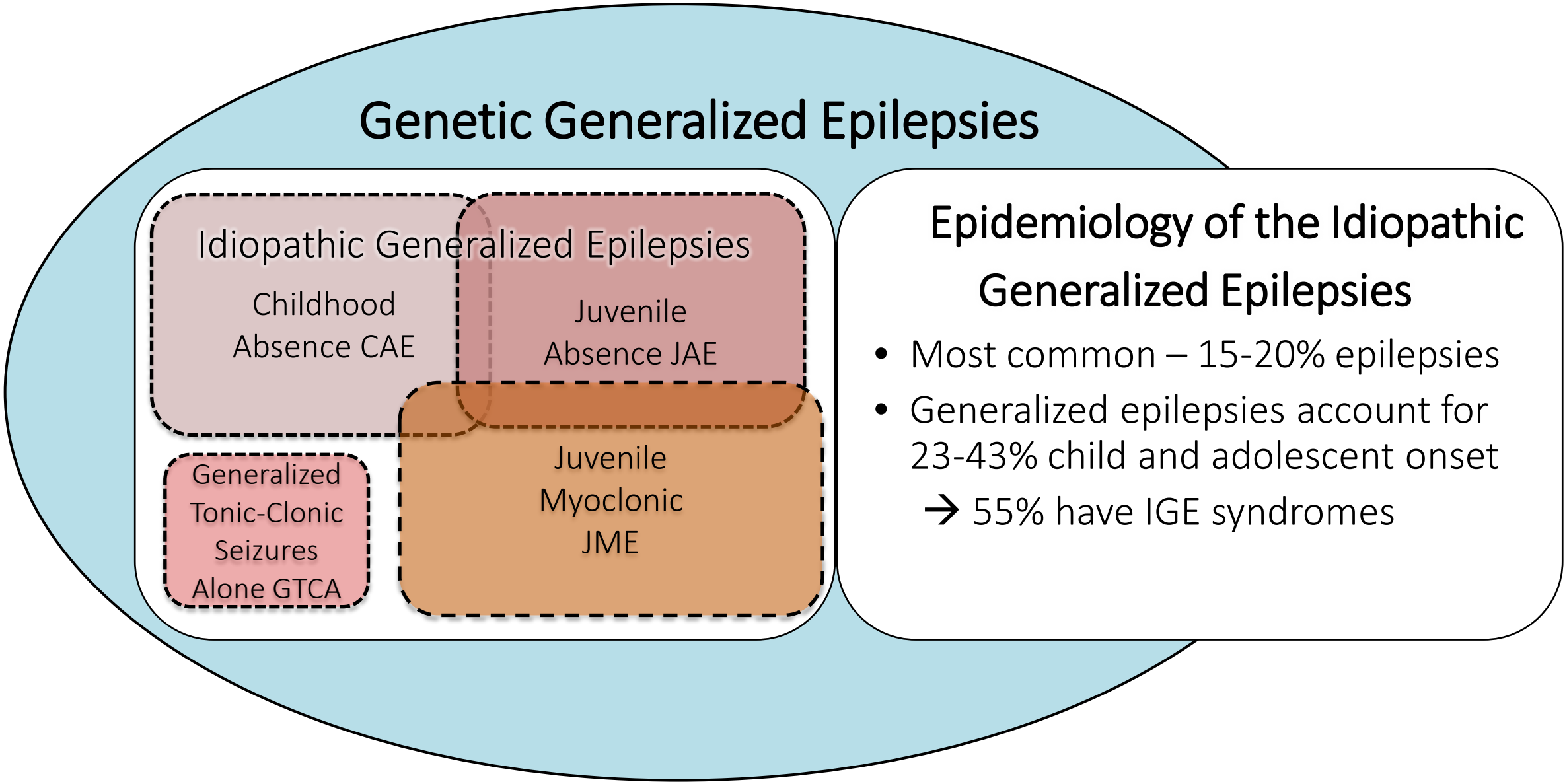

Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies
Childhood
Absence CAE
Juvenile
Absence JAE


Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies
Childhood
Absence CAE
Juvenile
Absence JAE
Juvenile
Myoclonic
JME


Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies
Childhood
Absence CAE
Juvenile
Absence JAE
Juvenile
Myoclonic
JME
Generalized
Tonic-Clonic
Seizures
Alone GTCA



Jallon et al 2005; Berg et al 1999, Wirrell et al 2011

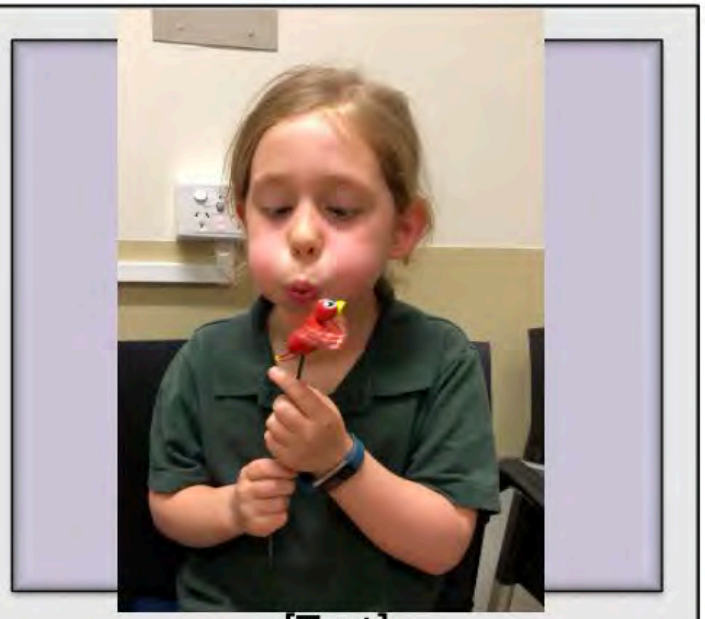


Epidemiology of the Idiopathic Generalized Epilepsies

- Most common – 15-20% epilepsies
- Generalized epilepsies account for 23-43% child and adolescent onset
  → 55% have IGE syndromes

Jallon et al 2005; Berg et al 1999, Wirrell et al 2011

IGE Seizure types



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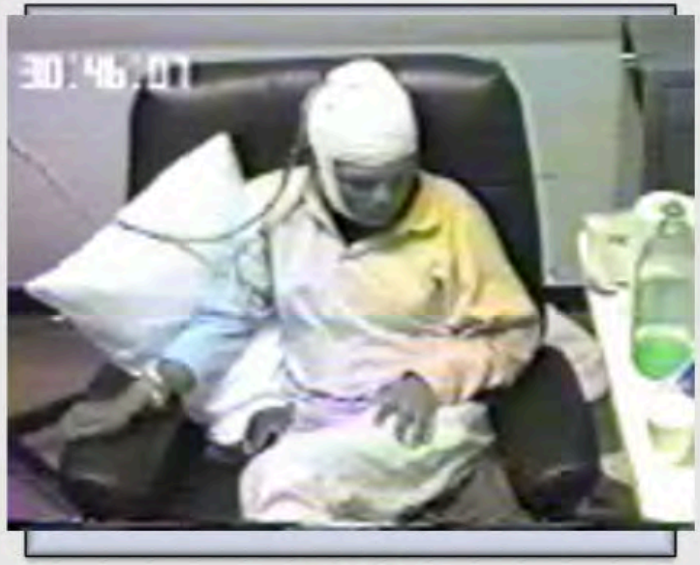
Absence



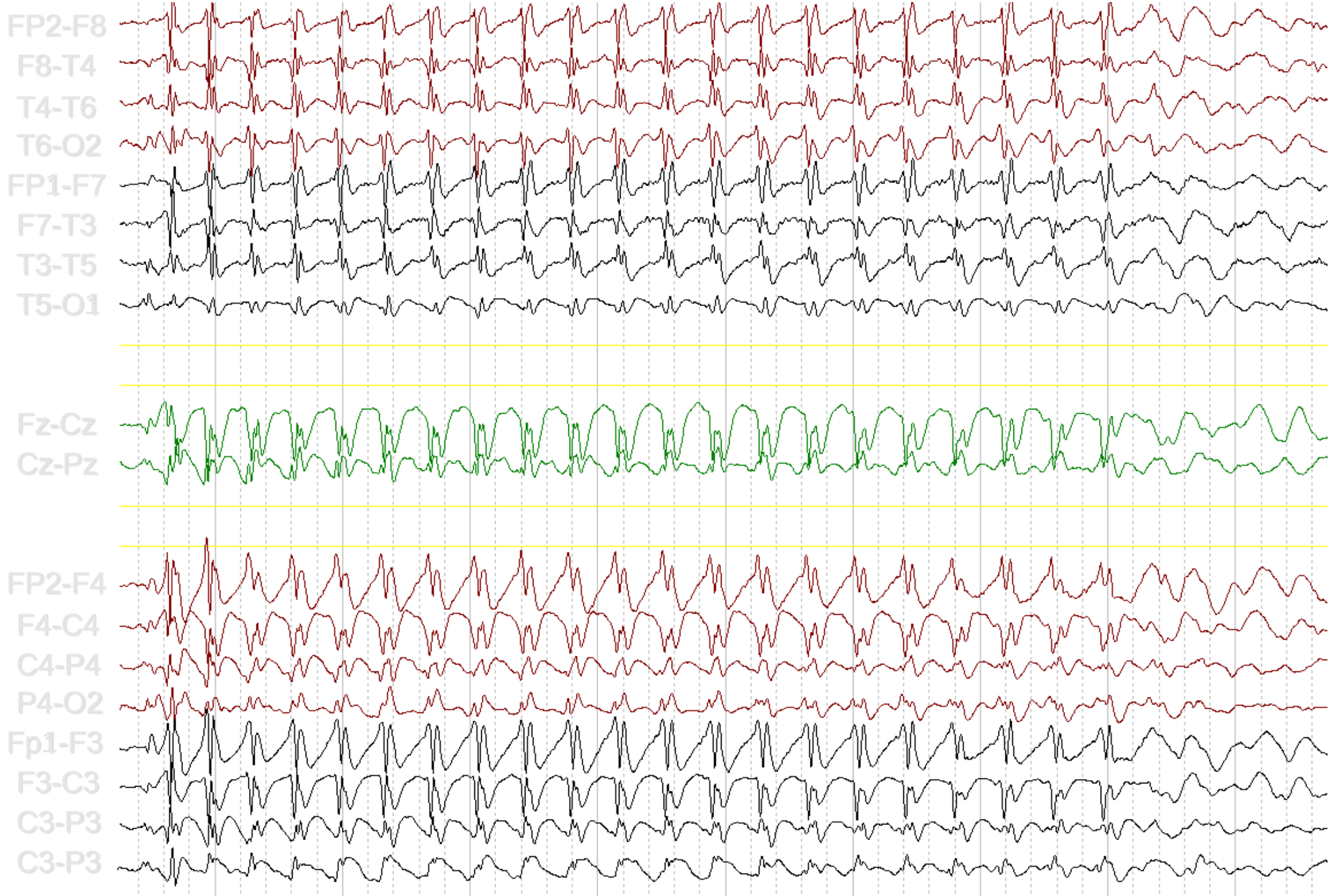
[Text]

Myoclonus

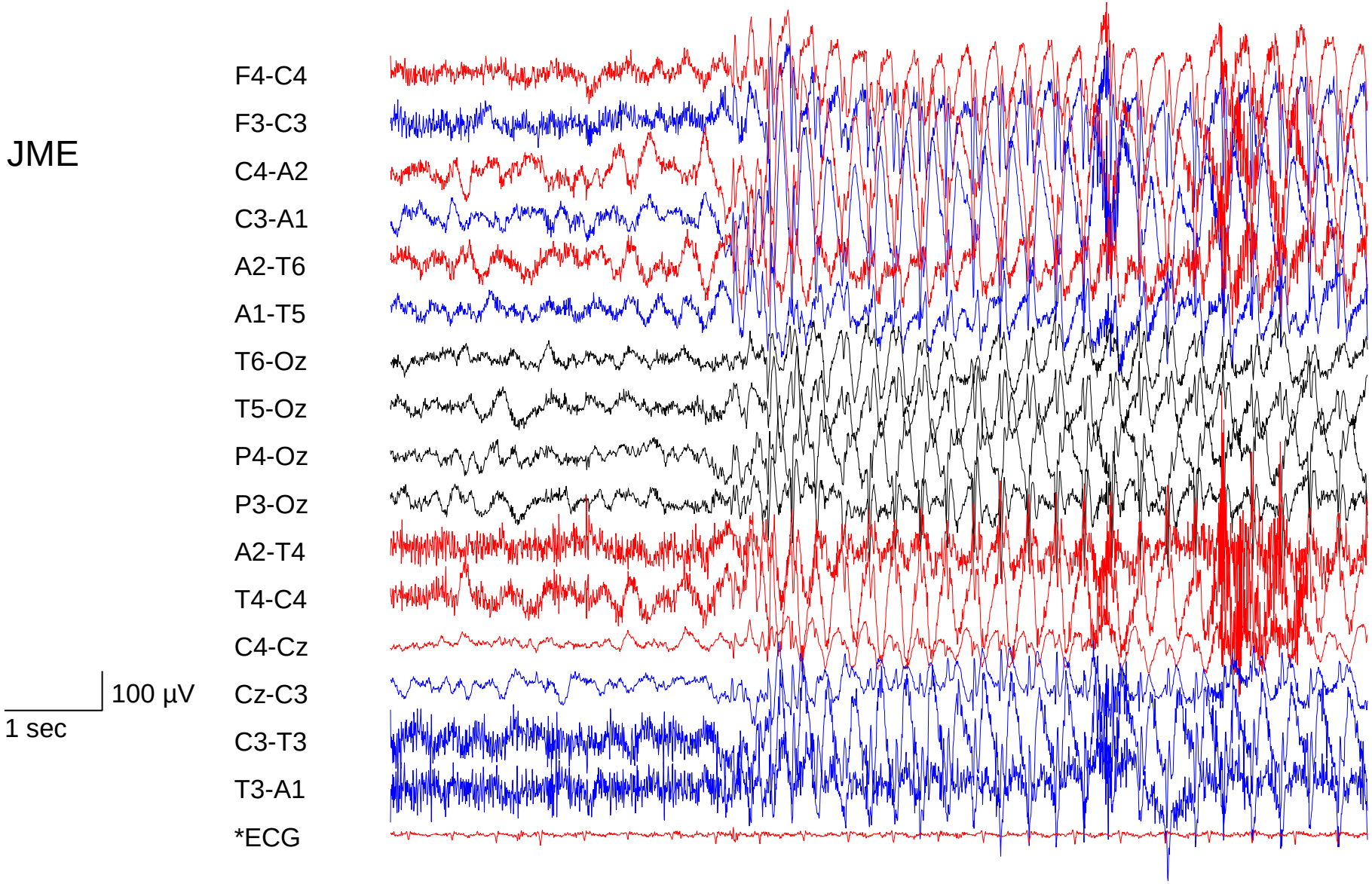
[Text]

Generalized tonic-clonic
Myoclonic-tonic-clonic

Seizure types NOT present in IGE:
tonic, atonic, myoclonic-atonic, focal, epileptic spasms

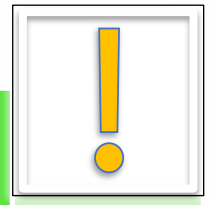

FP2-F8
F8-T4
T4-T6
T6-O2
FP1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
FP2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
C3-P3

JME


F4-C4
F3-C3
C4-A2
C3-A1
A2-T6
A1-T5
T6-Oz
T5-Oz
P4-Oz
P3-Oz
A2-T4
T4-C4
C4-Cz
Cz-C3
C3-T3
T3-A1
*ECG
100 µV
1 sec

Childhood Absence Epilepsy

- Typical absence seizures
- Paroxysms of 3 Hz (2.5-4 Hz) generalized spike-wave at the start of the absence (may have been obtained historically)



- Seizures
  - GTCS prior to or during the period of frequent absence seizures
  - Staring spells with typical duration >30 seconds or with postictal change
  - Absences occurring <daily in untreated patient
- EEG
  - Consistent unilateral EEG
  - Lack of HV activat^{n} 2.5-4Hz
  - no EEG correlate to staring
  - Persistent slowing EEG
- 2-3 or 11-13 years
- Potentially relevant neuro abn
- Potentially relevant abnormal MRI

- < 2 or >13 yrs
- Any seizure types except GTC
- Diffuse background slowing on EEG
- Moderate to profound intellectual disability
- Cognitive stagnation or decline
- Low csf glucose and/or *SLC2A1* pathogenic variant

Juvenile Absence Epilepsy

- Typical absence seizures
- Paroxysms of 3-5.5 Hz generalized spike-wave (may have been obtained historically)

- Staring spells with duration >30 secs or postictal change
- Absence seizures > 10/day
- Lack of HV activated 3-5.5 Hz spike-wave
- EEG persistent slowing
- Mild ID
- Potentially relevant abn neuro
- Potentially relevant abn MRI
- *Lack of GTC over course in absence relevant ASMs*

- Other seizure types except GTC
- Consistent unilateral EEG
- Diffuse slowing
- No EEG correlate to typical spell
- <8 or >20
- Mod to profound ID
- Cognitive stagnation or decline
- Low csf glc and/or *SLC2A1* variant

Juvenile Myoclonic Epilepsy

- Myoclonic seizures
- 3-5.5 Hz generalized spike-wave or generalized polyspike-wave on EEG (may be obtained historically)

- GTC status epilepticus
- Consistent unifocal semiology
- Consistent unifocal myoclonus
- Onset 8-9 years or 25-40 years
- Mild ID
- Potentially relevant neuro abn
- Potentially relevant MRI abn

- Other Seizure types except GTC, typical absence
- Absent polyspike and spike wave with habitual myoclonic event
- Focal EEG slowing
- Unilateral EEG
- SW freq <2.5Hz
- Diffuse background EEG slowing
- Age at onset <8 yrs or >40 yrs
- Mod to profound ID

- *Progressive cognitive decline*
- *Progressive myoclonus with impaired fine motor function*

Epilepsy with Generalised Tonic Clonic Seizures Alone

- Generalised tonic clonic seizures
- 3-5.5 Hz generalized spike-wave or polyspike-wave on EEG (may be obtained historically)

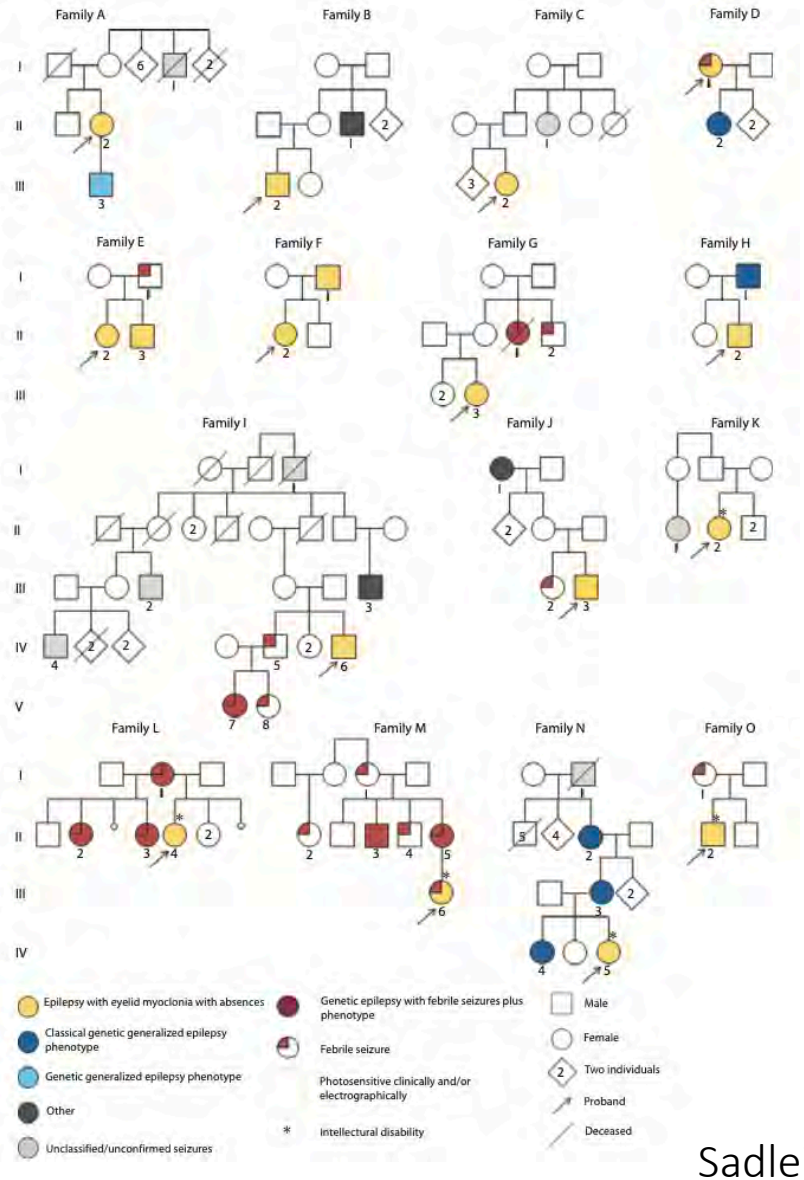
- Consistent unifocal semiology at seizure onset
- Age onset 5-9 or 26-40yr
- Mild ID
- Potentially relevant neuro abn
- Potentially relevant abn MRI

- Generalised MTC seizure, or any other seizure type
- EEG
- Focal slowing
- Consistent unilat abn
- Generalised SSW <2.5Hz
- Diffuse slowing
- Age onset <5 or >40
- Mod to profound ID
- Causative lesion on MRI
- *Progressive cognitive decline*

In resource limited regions, GTCA cannot be diagnosed without interictal EEG showing generalized spike wave, as one cannot exclude focal onset without EEG.

Family history in IGEs

- Most frequently negative
- Family history of mixed IGEs in relatives
- IGEs also in relatives of patients with
  - Epilepsy with Eyelid Myoclonia
  - Epilepsy with Myoclonic Absences
  - Myoclonic Epilepsy in Infancy
  - Genetic Epilepsy with Febrile Seizures Plus

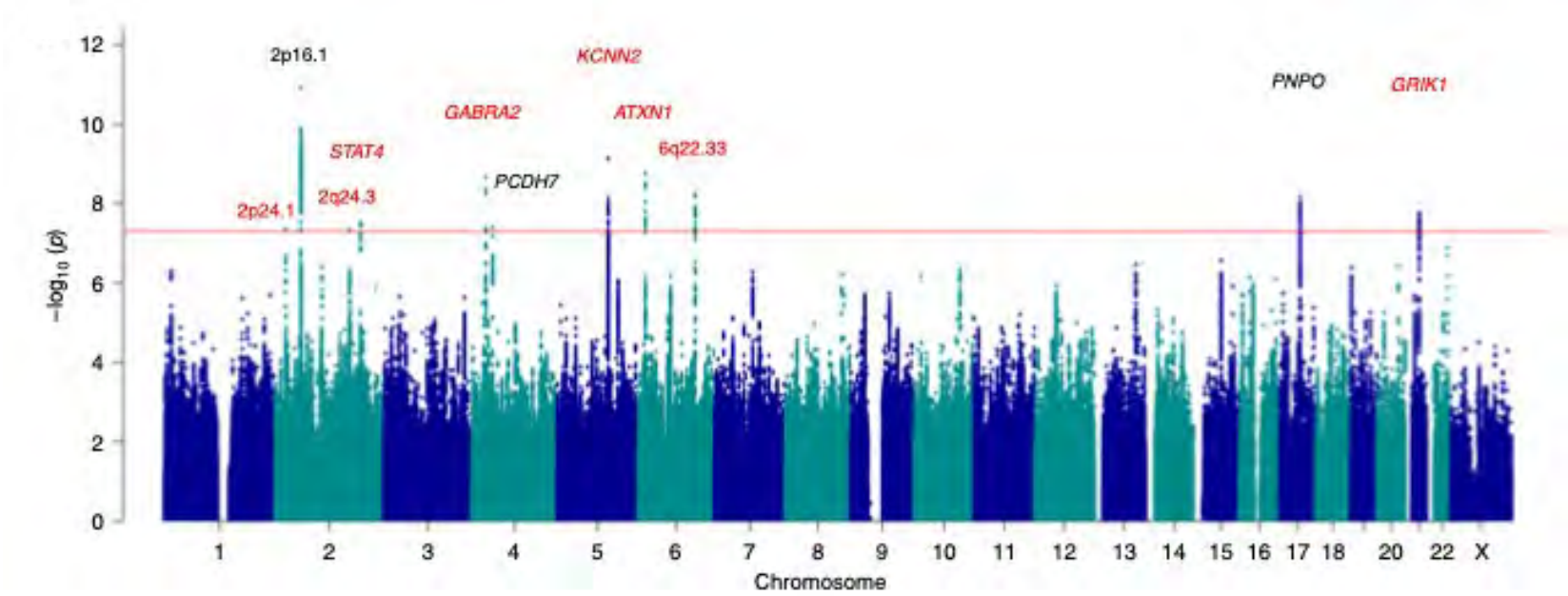


Sadleir et al 2012

Marini et al 2004; Bureau et al 2005;Auvin et al 2006; Zhang et al 2017

IGEs and GGEs have a genetic basis

- Complex inheritance – polygenic ± environmental factors



- De novo pathogenic variants eg. *SLC2A1, GABRG2, GABRA1*
- Copy number variants 3% – recurrent eg. 15q13.3 deletion

ILAE Consortium 2018, Arsov et al 2012, Wallace et al 2001, Helbig et al 2009

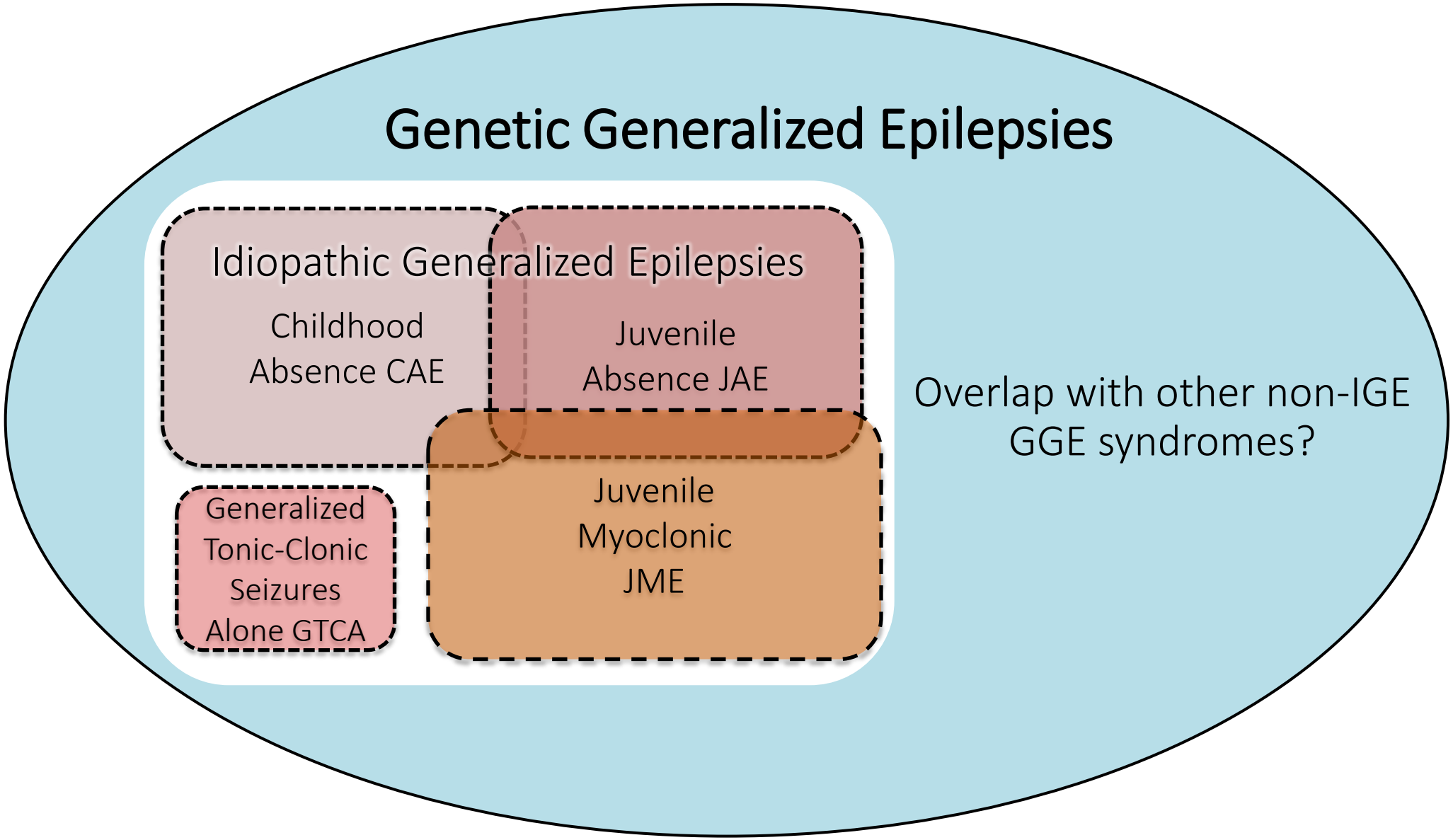
Anti-Seizure Medications

Valproate **most** effective –

- *not* in women of child-bearing age

Contraindicated

- Sodium channel blockers
  - X Carbamazepine, Oxcarbazepine, eslicarbazepine
  - X Phenytoin
  - Lamotrigine – use cautiously
- GABAergic drugs exacerbate absence and myoclonus
  - X Tiagabine, Vigabatrin


Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies
Childhood
Absence CAE
Juvenile
Absence JAE
Juvenile
Myoclonic
JME
Generalized
Tonic-Clonic
Seizures
Alone GTCA
Overlap with other non-IGE
GGE syndromes?

Genetic Generalized Epilepsies

Idiopathic Generalized Epilepsies

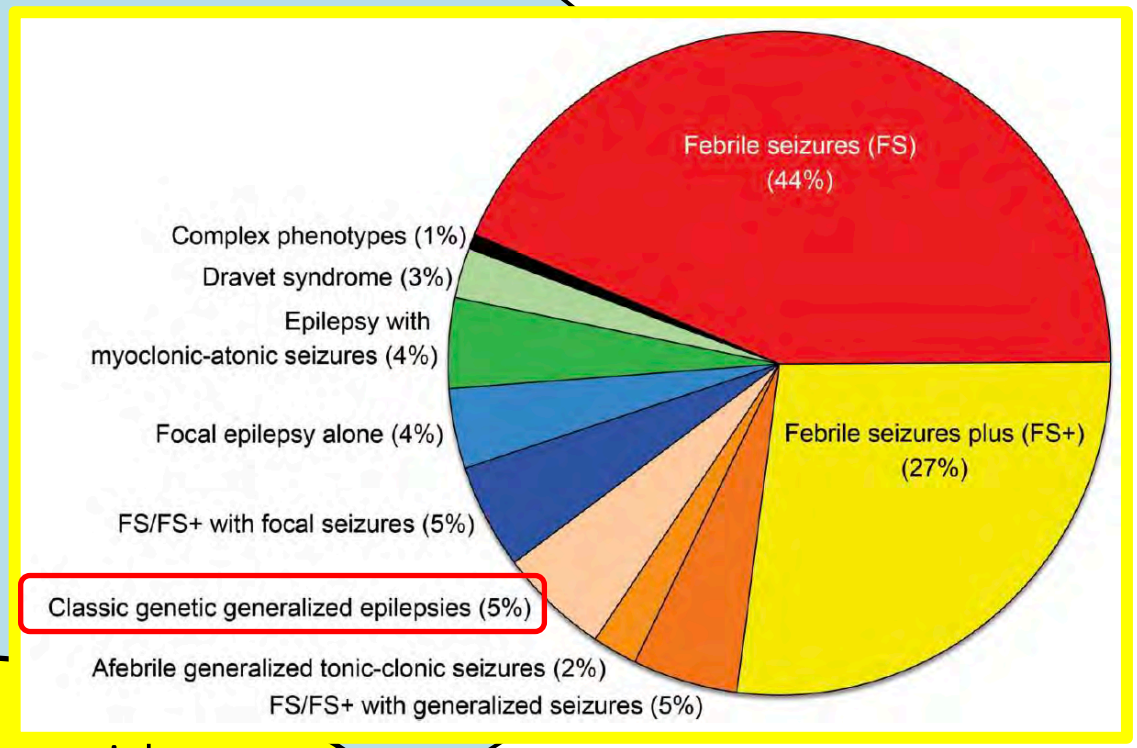
Childhood
Absence CAE

Juvenile
Absence JAE

Juvenile
Myoclonic
JME

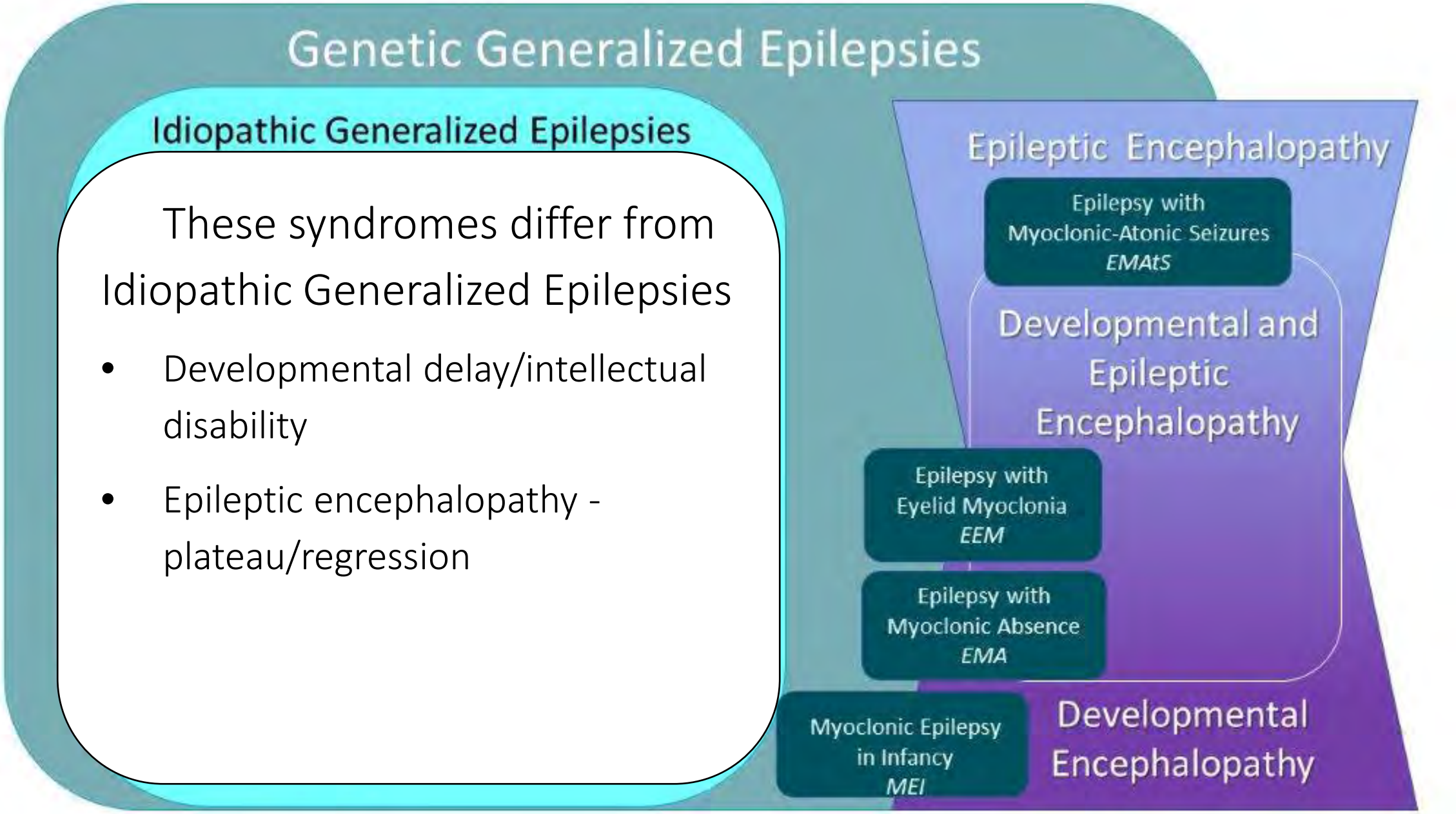
Generalized
Tonic-Clonic
Seizures
Alone GTCA

Genetic Epilepsy with
Febrile Seizures Plus
GEFS +



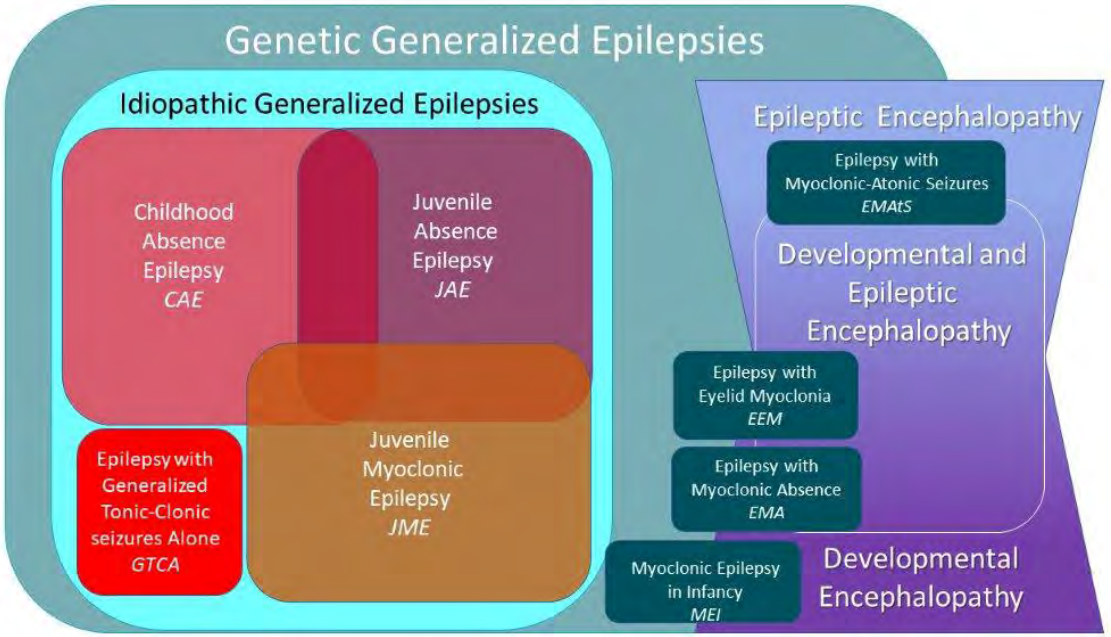
Zhang et al 2017

Scheffer and Berkovic 1997


Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies
These syndromes differ from Idiopathic Generalized Epilepsies
• Developmental delay/intellectual disability
• Epileptic encephalopathy - plateau/regression
Epileptic Encephalopathy
Epilepsy with Myoclonic-Atonic Seizures
EMAtS
Developmental and Epileptic Encephalopathy
Epilepsy with Eyelid Myoclonia
EEM
Epilepsy with Myoclonic Absence
EMA
Myoclonic Epilepsy in Infancy
MEI
Developmental Encephalopathy

The IGEs

- 4 syndromes, a subset of genetic generalised epilepsies
  - Childhood Absence Epilepsy,
  - Juvenile Absence Epilepsy,
  - Juvenile Myoclonic Epilepsy
  - Epilepsy with Generalized Tonic Clonic Seizures Alone,
- Polygenic inheritance, with or without environmental factors.
- Development is typically normal
  - mood disorders, ADHD and learning disabilities are common comorbidities.
- Seizure types include one, or a combination, of the following: absence, myoclonic, tonic-clonic and myoclonic-tonic-clonic seizures.
- The EEG shows generalized 2.5-5.5 Hz spike-wave which may be activated by hyperventilation or photic stimulation.



ILAE Definition of the Idiopathic Generalized Epilepsy Syndromes: Position Statement by the ILAE Task Force on Nosology and Definitions

Edouard Hirsch[1], Jacqueline French[2], Ingrid E Scheffer[3], Sameer M Zuberi[4], Eugen Trinka[5,6], Nicola Specchio[7], Ernest Somerville[8], Paulinea Samia[9], Kate Riney[10], Rima Nabbout[11], Satish Jain[12], Alicia Bogacz[13], Taoufik Alsaadi[14], Jo M Wilmshurst[15], Stephane Auvin[16], Samuel Wiebe[17], Paolo Tinuper[18,19]*, Elaine C Wirrell[20]*

Are IGEs and GGEs synonymous?

- IGEs are a subgroup of the GGEs
- Specific syndrome details – see ILAE website
- Overlap intriguing from a biological perspective